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VOL. VI

JANUARY, APRIL, JULY, OCTOBER, 1922

ST. LOUIS  
C. V. MOSBY COMPANY  
1922

437125  
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# The American Journal of Syphilis

A QUARTERLY JOURNAL DEVOTED TO THE  
STUDY AND PREVENTION OF SYPHILIS

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VOL. VI.

ST. LOUIS, JANUARY, 1922

No. 1

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## Original Articles

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### THE INFLUENCE UPON TOXICITY AND TRYPANOCIDAL ACTIVITY OF SHAKING ACID AND ALKALINIZED SOLUTIONS OF ARSPHENAMINE AND SOLU- TIONS OF NEOARSPHENAMINE IN AIR\*

BY JAY FRANK SCHAMBERG, M.D., JOHN A. KOLMER, M.D., AND  
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(Received for publication, January 10, 1922)

IT IS a well established fact that oxidation of arsphenamine increases the toxicity by conversion of part of the drug to the poisonous aminohydroxyphenylarsenoxid (arsenoxide). This observation was early insisted upon by Ehrlich and his collaborators, who urged against unnecessary shaking and also upon prompt use of the drug after it was put into solution. Inasmuch as arsphenamine and its derivative neoarsphenamine are used in large clinics upon scores of patients, and various technics are carried out for the purpose of economizing time, it is of interest to determine whether some of these methods exert any influence upon the toxicity of the drug and upon its therapeutic effect.

Roth (Public Health Report, Vol. 35, No. 38, Sept. 17, 1920) stud-

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\*From the Dermatological Research Institute (Work carried out by the aid of funds accruing from the sale of the arsphenamine).

ied the effect of shaking alkalinized aqueous solutions of arsphenamine and aqueous solutions of neoarsphenamine in the presence of air. He found that shaking alkalinized aqueous solutions of arsphenamine for ten minutes in the presence of air caused changes both in their color and in their toxicity. The toxicity was increased about 60 per cent.

With the ordinary lot of arsphenamine it is of course unnecessary to shake the solution after the alkali has been added, although Roth states that he has often handled samples of arsphenamine, which upon addition of alkali to their aqueous solutions, formed dense precipitates that redissolved only after considerable shaking.

Of more practical value, it appears to us, is the influence of prolonged shaking upon the acid aqueous solutions of arsphenamine.

#### TECHNIC OF TOXICITY TESTS

In conducting these tests the technic described by Dr. Roth<sup>1</sup> was employed except that rats received increasing amounts of drug per kilo of body weight instead of giving a series of rats the same amount per body weight and calculating changes in toxicity according to the percentage of animals succumbing within a certain period of time.

Arsphenamine and neoarsphenamine prepared by four different laboratories were employed in these experiments, designated respectively H. K. R. T. and U.

While Dr. Roth conducted his experiments with alkalinized solutions of arsphenamine our tests were made with both acid and alkalinized solutions of arsphenamine as follows:

*Acid solutions* were prepared by dissolving 0.5 gm. arsphenamine in 21 c.c. of sterile water with the minimum of shaking. Three such solutions were prepared with each compound. The first solution was alkalinized with 4 c.c. of normal sodium hydroxide and injected at once; 10 c.c. of the second solution were placed in a 25 c.c. glass stoppered cylinder, shaken vigorously for one minute (about 254 times), alkalinized and injected. Ten c.c. of the third solution were placed in a 25 c.c. cylinder, shaken vigorously for ten minutes, alkalinized and injected.

White rats were injected intravenously with each solution in doses ranging from 0.080 to 0.130 gm. per kilo.

*Two per cent alkalinized solutions of arsphenamine* were prepared



in a similar manner by dissolving 0.4 gm. in 21 c.c. warm sterile distilled water and after complete solution adding 4 c.c. of normal sodium hydroxide. A portion of this solution was injected at once in amounts varying from 0.080 to 0.130 per kilogram of weight. A second portion of 10 c.c. was shaken in a 25 c.c. cylinder for one minute (about 250 times) and injected into a second series; a third portion of 10 c.c. was shaken in a 25 c.c. cylinder for ten minutes and injected in similar amounts.

It is important in the interpretation of the results to realize that the shaking of one and ten minutes respectively was *additional* shaking, beyond the time necessary to effect a proper solution of the drug.

Table I shows the effect of such extra shaking: with arsphe-  
namine from Laboratory K the drug prepared in the usual manner was tolerated up to 120 mg. per kilo. After one minute's extra shaking

TABLE I  
INFLUENCE UPON TOXICITY OF SHAKING AQUEOUS ALKALINIZED SOLUTIONS OF  
ARSPHENAMINE (LAB. K)

WEIGHT	DOSE PER KILO	AMOUNT INJECTED	TIME OF INJECTION (SECONDS)	SOLUTION	RESULTS IN DAYS						
					1	2	3	4	5	6	7
100	.060	.30	38	Not shaken	—	—	—	—	—	—	—
100	.070	.35	43		—	—	—	—	—	—	—
125	.080	.50	60		—	—	—	—	—	—	—
90	.090	.41	50		—	—	—	—	—	—	—
90	.100	.45	54		—	—	—	—	—	—	—
80	.110	.44	53		—	—	—	—	—	—	—
80	.120	.48	57		—	—	—	—	—	—	—
100	.060	.30	38	Shaken one minute	—	—	—	—	—	—	—
100	.070	.35	43		—	—	—	—	—	—	—
100	.080	.40	48		—	—	—	—	—	—	—
90	.090	.41	50		—	—	—	—	—	—	—
80	.100	.40	48		D	—	—	—	—	—	—
85	.110	.46	52		D	—	—	—	—	—	—
85	.120	.51	61		—	D	—	—	—	—	—
125	.060	.38	45	Shaken ten minutes	—	—	—	—	—	—	—
95	.070	.33	39		—	D	—	—	—	—	—
95	.080	.38	46		—	D	—	—	—	—	—
115	.090	.52	62		—	—	—	—	—	—	—
85	.100	.43	49		D	D	—	—	—	—	—
80	.110	.44	53		D	—	—	—	—	—	—
85	.120	.51	61		D	—	—	—	—	—	—

of the *alkaline* solution, the drug was only tolerated in 90 mg. per kilo. After ten minutes' shaking the tolerated dose was only 60 mg. per kilo.

Table II gives the results of shaking acid solution of arspheamine. The drug prepared in the usual way (Laboratory H) was tolerated in 110 mg. per kilo. At the end of one minute's shaking, the tolerated dose was 100 mg. and at the end of ten minutes further shaking, 80 mg.

TABLE II  
INFLUENCE UPON TOXICITY OF SHAKING AQUEOUS ACID SOLUTIONS OF  
ARSPHENAMINE (LAB. H) FOLLOWED BY ALKALINIZATION

WEIGHT	DOSE PER KILO	AMOUNT INJECTED	TIME OF INJECTION (SECONDS)	SOLUTIONS	RESULTS IN DAYS						
					1	2	3	4	5	6	7
110	.080	.44	52	Not shaken	—	—	—	—	—	—	—
90	.090	.41	49		—	—	—	—	—	—	—
90	.100	.45	54		—	—	—	—	—	—	—
90	.110	.50	60		—	—	—	—	—	—	—
85	.120	.51	61		—	D					
85	.130	.55	66		D						
95	.080	.38	45	Shaken one minute	—	—	—	—	—	—	—
90	.090	.41	49		—	—	—	—	—	—	—
85	.100	.43	51		—	—	—	—	—	—	—
110	.110	.55	66		—	D					
95	.120	.57	68		—	D					
85	.130	.55	66		D						
95	.080	.38	49	Shaken ten minutes	—	—	—	—	—	—	—
95	.090	.43	51		D						
105	.100	.53	63		D						
95	.110	.52	62		—	D					

In Table III, the product of another laboratory (R) was shaken in aqueous solution. The figures were 130 mg. for the original solution, 130 mg. after one minute's shaking and 90 mg. after ten minutes' extra shaking.

In Table IV, (Product of Lab. R) no increase in toxicity was evident after one and ten minutes experimental shaking.

In order to study the assembled results of these experiments a summary of the tests is presented in Table V.

From these experiments, it is evident that while shaking of the acid solution tends after a time to increase the toxicity of the prod-

uct it is noted that the increase in toxicity is not nearly so great as occurs when *alkaline* solutions are shaken. Five compounds from three different laboratories were tolerated on the average in 121 mg. per kilo; after one minute's extra shaking, the average tolerated dose was 118 mg., and after ten minutes' shaking 98 mg.

The experiments indicate, however, that certain products can be experimentally shaken with less liability to oxidation and increased toxicity than others. Three lots from Lab. R gave the following figures: 123 mg. when prepared in the usual way; after one minute's extra shaking, 123 mg.; after ten minutes' extra shaking, 110 mg.

It is seen, therefore, that whereas the average of the five products from three laboratories increased in toxicity  $2\frac{1}{2}$  per cent after one minute's shaking and 19 per cent after ten minutes' shaking, the average of the three products from Lab. R did not increase in toxicity after one minute's extra shaking, and increased but 10 per cent after ten minutes' shaking.

TABLE III  
INFLUENCE UPON TOXICITY OF SHAKING AQUEOUS ACID SOLUTIONS OF  
ARSPHENAMINE (LAB. R) FOLLOWED BY ALKALINIZATION

WEIGHT (GM)	DOSE PER KILO	AMOUNT INJECTED	TIME OF INJECTION (SECONDS)	SOLUTIONS	RESULTS IN DAYS						
					1	2	3	4	5	7	
130	.090	.59	70	Prepared in usual manner	—	—	—	—	—	—	
125	.100	.63	75		—	—	—	—	—	—	
105	.110	.58	69		—	D	—	—	—	—	
115	.120	.69	83		—	—	—	—	—	—	
110	.130	.72	86		—	—	—	—	—	—	
110	.140	.77	89		—	—	—	—	—	—	
130	.090	.59	69	Shaken one minute extra	—	—	—	—	—	—	
150	.100	.75	90		—	—	—	—	—	—	
150	.110	.83	100		—	—	—	—	—	—	
160	.120	.90	114		—	D	—	—	—	—	
140	.130	.91	109		—	—	—	—	—	—	
110	.140	.77	89		—	—	—	—	—	—	
105	.090	.47	56	Shaken ten minutes extra	—	—	—	—	—	—	
115	.100	.58	69		—	—	D	—	—	—	
95	.110	.52	62		—	D	—	—	—	—	
110	.120	.66	82		—	—	—	—	—	—	
100	.130	.65	81		—	D	—	—	—	—	
115	.140	.81	100		—	D	—	—	—	—	

At rate of approximately 250 times per minute.

TABLE IV  
INFLUENCE UPON TOXICITY OF SHAKING AQUEOUS ACID SOLUTIONS OF  
ARSPHENAMINE (LAB. R) FOLLOWED BY ALKALINIZATION

WEIGHT (GM)	DOSE PER KILO	AMOUNT INJECTED	TIME OF INJECTION	SOLUTIONS	RESULTS IN DAYS					
					1	2	3	4	5	7
120	.090	.54	64	Not shaken	—	—	—	—	—	—
125	.100	.63	75		—	—	—	—	—	—
120	.110	.66	82		—	—	—	—	—	—
110	.120	.66	82		—	—	—	—	—	—
160	.130	.72	86		—	—	—	—	—	—
115	.140	.81	97		—	—	D	—	—	—
140	.090	.63	75	Shaken one minute	—	—	—	—	—	—
120	.100	.60	72		—	—	—	—	—	—
120	.110	.66	82		—	—	—	—	—	—
125	.120	.75	90		—	—	—	—	—	—
120	.130	.78	93		—	D	—	—	—	—
110	.140	.77	92		—	—	—	—	—	—
135	.090	.61	73	Shaken ten minutes	—	—	—	—	—	—
120	.100	.60	72		—	—	—	—	—	—
135	.110	.74	89		—	—	—	—	—	—
140	.120	.84	104		—	—	—	—	—	—
115	.130	.75	90		—	—	—	—	—	—
115	.140	.81	100		—	D	—	—	—	—

TABLE V  
SUMMARY SHOWING INFLUENCE OF SHAKING ACID SOLUTIONS OF  
ARSPHENAMINE IN AIR FOLLOWED BY ALKALINIZATION

PRODUCT OF LABORATORY	HIGHEST TOLERATED DOSES PER KILO		
	INJECTED AT ONCE	SHAKEN ONE MINUTE	SHAKEN TEN MINUTES
H	.110	.100	.80
K	.120 - .130	.130	.100
R	.110	.100	.90 - .110
R	about .130	about .130	about .90 - .110
R	about .130	about .130	about .130

TABLE VI  
SUMMARY SHOWING INFLUENCE OF SHAKING ALKALINIZED SOLUTIONS  
OF ARSPHENAMINE IN AIR

PRODUCT OF LABORATORY	HIGHEST TOLERATED DOSES PER KILO		
	INJECTED AT ONCE	SHAKEN ONE MINUTE	SHAKEN TEN MINUTES
H	.080 - .100	.120	.090
K	.120	.090	.060
R	.120	.120	.100
Average Increase in Toxicity		0	25%

## NEOARSPHENAMINE

Inasmuch as different market preparations of neoarsphenamine vary somewhat in solubility, we have, following the example of Roth, tested the influence of shaking in the presence of air. As Roth very correctly states, certain lots of neoarsphenamine which were readily soluble in water when manufactured, later became difficult to dissolve. These products have evidently undergone some intramolecular change with consequent increase in toxicity. To dissolve such products it becomes necessary to shake for some time or to allow them to stand for a much longer period than usual. We have carried out our tests on the influence of shaking upon toxicity as follows:

Four per cent solutions of neoarsphenamine were prepared by dissolving one gram in 25 c.c. sterile distilled water. A portion was injected at once in amounts varying from 160 to 250 mg. per kilogram of weight. A second portion of 10 c.c. was placed in a 25 c.c. cylinder, shaken vigorously (about 250 times) for one minute and injected in similar amounts; a third portion of 10 c.c. was placed in a 25 c.c. cylinder, shaken vigorously for ten minutes and injected into a third series of animals.

In all of these tests white rats were employed taken from the same stock and similar as to weight and condition. The rate of injection was the same for all solutions, being 0.5 c.c. per minute; all injections were given into the saphenous vein by the gravity method employed in our regular toxicity tests.<sup>2</sup>

In Table VII, the figures on product of Lab. R are given. It is observed that the fresh solution is tolerated for seven days (the period of the U. S. official tests) in the dose of 200 mg. per kilo. After one minute's extra shaking, while some of the animals live for five days, none survive for seven days even at 160 mg. After ten minutes' shaking, not even 60 mg. are tolerated. In the summary (Table VIII) it is seen that products from two other laboratories have fared better, but there is nevertheless a great increase in toxicity on shaking. The product of Lab. R showed an increase in toxicity of 70 per cent after ten minutes' shaking; that of Laboratory H, an increase of 60 per cent and that of Lab. T, an increase of 20 per cent. But what is more significant and more important, even after one minute's extra shaking there was an increase in toxicity of 20 per cent, 5 per cent and 20 per cent, respectively. Roth like-

wise found a distinct increase in toxicity upon shaking neoarsphenamine in the presence of air for one minute and an enormous increase when shaken for ten minutes.

As in the case of arsphenamine, the behavior of different lots of neoarsphenamine exhibits great variations in results, but the experiments all indicate the same tendency to increase in toxicity on shaking.

#### TRYPANOCIDAL TESTS

While Ehrlich, Roth and others have called attention to the influence of shaking on the toxicity of solutions of arsphenamine

TABLE VII  
THE INFLUENCE OF SHAKING AQUEOUS SOLUTIONS OF NEOARSPHENAMINE (LAB. R)  
IN AIR

WEIGHT	DOSE PER KILO	AMOUNT SOLUTION INJECTED	TIME OF INJECTION (SECONDS)	SOLUTION	RESULTS IN DAYS						
					1	2	3	4	5	6	7
170	.160	.68	88	Not Shaken	—	—	—	—	—	—	—
150	.180	.68	88		—	—	—	—	—	—	—
140	.190	.67	80		—	—	—	—	—	—	—
100	.200	.50	60		—	—	—	—	—	—	—
115	.210	.60	72		—	—	—	—	—	—	D
165	.220	.91	109		—	—	—	—	D	—	—
120	.240	.72	86		—	—	—	—	D	—	—
235	.160	.92	110	Shaken one minute	—	—	—	—	—	D	—
135	.180	.59	70		—	—	—	—	D	—	—
150	.190	.71	85		—	—	—	—	—	D	—
100	.200	.50	60		—	—	—	—	—	D	—
130	.210	.68	82		—	D	—	—	—	—	—
80	.220	.44	52		—	D	—	—	—	—	—
100	.240	.60	72		—	D	—	—	—	—	—
155	.060	.23	27	Shaken ten minutes	—	—	—	—	D	—	—
125	.100	.32	38		D	—	—	—	—	—	—
145	.120	.44	52		D	—	—	—	—	—	—
200	.160	.76	91		D	—	—	—	—	—	—

TABLE VIII  
SUMMARY SHOWING INFLUENCE OF SHAKING SOLUTIONS OF  
NEOARSPHENAMINE IN AIR

PRODUCT OF LABORATORY	HIGHEST TOLERATED DOSES PER KILO		
	INJECTED AT ONCE	SHAKEN ONE MINUTE	SHAKEN TEN MINUTES
H	.200	.190	.080
T	.250	.200	.200
R	.200	less than .160	less than .060

and neoarsphenamine, but little work has been done on the effect upon the therapeutic properties of such solutions. As stated elsewhere, we had found the trypanosoma equiperdum an excellent test parasite for the determination of the therapeutic properties of the arsenobenzenes. Where similar tests have been carried out on the Spirocheta pallida in rabbits a considerable degree of parallelism has been demonstrated.

In Table IX, the influence of shaking is shown upon the *alkalinized* solution of arsphenamine.

Table X, presents the results of shaking upon the *acid* solutions of arsphenamine.

Tables XI and XII indicate the effect of shaking upon solutions of neoarsphenamine.

The results in the accompanying tables are summarized in Tables

TABLE IX  
INFLUENCE UPON TRYpanOCIDAL ACTIVITY OF SHAKING ALKALINIZED SOLUTIONS OF ARSPHENAMINE (LAB. R)

SOLUTIONS	WEIGHT	DOSE PER KILO	RESULTS IN DAYS											
			1	2	3	4	5	6	7	9	11	14		
Not shaken beyond the time necessary to dissolve	215	2 mg.	*—	—	—	—	—	+	+	D	D			
	190	4 "	—	—	—	—	—	—	+	+	D			
	325	6 "	—	—	—	—	—	—	—	—	—	—		
	220	8 "	—	—	—	—	—	—	—	—	—	—		
	245	10 "	—	—	—	—	—	—	—	—	—	—		
	240	12 "	—	—	—	—	—	—	—	—	—	—		
Shaken One minute extra	235	2 mg.	—	—	—	—	—	—	—	—	—	—		
	195	4 "	—	—	—	—	—	—	—	—	—	—		
	250	6 "	—	—	—	—	—	—	—	—	—	—		
	215	8 "	—	—	—	—	—	—	—	—	—	—		
	195	10 "	—	—	—	—	—	—	—	—	—	—		
	205	12 "	—	—	—	—	—	—	—	—	—	—		
Shaken ten minutes extra	185	2 mg.	—	—	—	—	—	—	—	—	—	—	+	
	175	4 "	—	—	—	—	—	—	—	—	—	—	+	
	150	6 "	—	—	—	—	—	—	—	—	—	—	—	
	155	8 "	—	—	—	—	—	—	—	—	—	—	—	
	205	10 "	—	—	—	—	—	—	—	—	—	—	—	
	165	12 "	—	—	—	—	—	—	—	—	—	—	—	
Controls	150	—	+	+	+	D								
	145	—	+	+	+	D								
	125	—	+	+	+	D								
	150	—	+	+	+	D								

\* — = No trypanosomes in tail blood; + = trypanosomes present; D = death from trypanosomiasis.

XIII and XIV. They demonstrate the very interesting observation that *solutions of arsphenamine after being shaken experimentally for one minute extra acquire an increased trypanocidal activity*. Whereas the average number of milligrams necessary to sterilize animals (Table XIII) was originally 4, after one minute's shaking, the average amount was 2.66 mg. At the end of ten minutes' shaking of acid solutions, however, there was some decrease in trypanocidal effect. When alkalinized solutions of arsphenamine were shaken the increase in trypanocidal effect persisted even after ten minutes' shaking (Table XIV).

Solutions of neoarsphenamine did not exhibit any material change in trypanocidal influence after one minute or ten minutes of shaking.

TABLE X

INFLUENCE UPON TRYPANOCIDAL ACTIVITY OF SHAKING ACID SOLUTIONS OF ARSPHENAMINE (LAB. T) FOLLOWED BY ALKALINIZATION AND INJECTION INTO RATS

SOLUTIONS	WEIGHT	DOSE PER KILO	RESULTS IN DAYS										
			1	2	3	4	5	6	7	9	11	14	
Not shaken beyond the time necessary to dissolve	125	1 mg.	—	+	+	+	D						
	120	2 "	—	—	—	—	—	—	—	—	+	+	
	120	4 "	—	—	—	—	—	—	—	—	—	—	
	120	6 "	—	—	—	—	—	—	—	—	—	—	
	125	8 "	—	—	—	—	—	—	—	—	—	—	
	120	10 "	—	—	—	—	—	—	—	—	—	—	
Shaken one minute extra	125	1 mg.	—	+	+	+	D						
	130	2 "	—	—	—	—	—	—	—	—	—	—	
	130	4 "	—	—	—	—	—	—	—	—	—	—	
	120	6 "	—	—	—	—	—	—	—	—	—	—	
	130	8 "	—	—	—	—	—	—	—	—	—	—	
	140	10 "	—	—	—	—	—	—	—	—	—	—	
Shaken ten minutes extra	125	1 mg.	+	+	+	+	D						
	135	2 "	—	—	—	—	—	+	+	+	D		
	140	4 "	—	—	—	—	—	+	+	+	D		
	130	6 "	—	—	—	—	—	—	—	—	—	—	
	125	8 "	—	—	—	—	—	—	—	—	—	—	
	120	10 "	—	—	—	—	—	—	—	—	—	—	
Controls	130	—	+	+	+	+	D						
	130	—	+	+	+	+	D						
	140	—	+	+	+	+	D						
	125	—	+	+	+	+	D						

\* Died on 16th day.



## CHEMICAL CONSIDERATIONS

Several of the lots of arspenamine and neoarsphenamine that were examined for trypanocidal activity were tested chemically after experimental shaking to determine the amount of oxidation that had actually taken place.

Preparation of arspenamine No. 5092 was dissolved in water and one-tenth normal iodine solution added drop by drop. Arspenamine on account of the trivalent condition of the arsenic takes up iodine quantitatively being oxidized to the corresponding arsonic acid derivative. Based on this reaction, it is possible to determine quantitatively the oxygen requirements of arspenamine (see a paper by Raiziss and Proskouriakoff, *The Chemistry of Arspenamine and Its Relation to Toxicity, Arch. Dermat. and Syph.*, 1920, ii, No. 3, 280; also the Chemistry of Neoarsphenamine and Its Relation

TABLE XI  
THE INFLUENCE UPON TRYPANOCIDAL ACTIVITY OF SHAKING SOLUTIONS OF  
NEOARSPHENAMINE (LAB. 7) IN AIR

SOLUTIONS	WEIGHT	DOSE PER KILO	RESULTS IN DAYS										
			1	2	3	4	5	6	7	9	11	14	
Not shaken	110	1 mg.	+	+	+	D							
	135	2 "	-	-	-	+	+	+	+	D			
	130	4 "	-	-	-	-	-	-	-	-	-	-	
	120	6 "	-	-	-	-	-	-	-	-	-	-	
	120	8 "	-	-	-	-	-	-	-	-	-	-	
	125	10 "	-	-	-	-	-	-	-	-	-	-	
Shaken one minute	140	1 mg.	+	+	+	D							
	130	2 "	-	-	-	-	+	+	+	D			
	130	4 "	-	-	-	-	-	-	-	-	-	-	
	120	6 "	-	-	-	-	-	-	-	-	-	-	
	120	8 "	-	-	-	-	-	-	-	-	-	-	
	120	11 "	-	-	-	-	-	-	-	-	-	-	
Shaken ten minutes	125	1 mg.	-	+	+	+	D						
	135	2 "	-	-	-	-	-	-	-	-	-	*	
	115	4 "	-	-	-	-	-	-	-	-	-	-	
	130	6 "	-	-	-	-	-	-	-	-	-	-	
	140	8 "	-	-	-	-	-	-	-	-	-	-	
	145	10 "	-	-	-	-	-	-	-	-	-	-	
Controls	130	-	+	+	+	+	D						
	130	-	+	+	+	+	D						
	150	-	+	+	+	+	D						
	125	-	+	+	+	+	D						

\* Developed trypanosomiasis on 17th day and died on 20th day.

TABLE XII  
THE INFLUENCE UPON TRYPANOCIDAL ACTIVITY OF SHAKING SOLUTIONS OF  
NEOARSPHENAMINE (LAB. R) IN AIR

SOLUTIONS	WEIGHT (GMS)	DOSE PER KILO	RESULTS IN DAYS											
			1	2	3	4	5	6	7	9	11	14		
Not shaken beyond the time necessary to dissolve	135	1 mg.	+	+	+	+	D							
	125	2 "	-	-	-	-	-	-	-	+	+	D		
	115	4 "	-	-	-	-	-	-	-	-	-	-		
	115	6 "	-	-	-	-	-	-	-	-	-	-		
	135	8 "	-	-	-	-	-	-	-	-	-	-		
	130	10 "	-	-	-	-	-	-	-	-	-	-		
Shaken one minute extra	125	1 mg.	+	+	+	D								
	130	2 "	-	-	+	+	+	+	+	D				
	125	4 "	-	-	-	-	-	-	-	-	-	-		
	120	6 "	-	-	-	-	-	-	-	-	-	-		
	120	8 "	-	-	-	-	-	-	-	-	-	-		
	130	10 "	-	-	-	-	-	-	-	-	-	-		
Shaken ten minutes extra	125	1 mg.	-	-	+	+	+	+	D					
	130	2 "	-	-	-	-	-	-	-	-	+	+		
	125	4 "	-	-	-	-	-	-	-	-	-	-		
	135	6 "	-	-	-	-	-	-	-	-	-	-		
	120	8 "	-	-	-	-	-	-	-	-	-	-		
	115	10 "	-	-	-	-	-	-	-	-	-	-		
Controls	130	-	+	+	+	+	D							
	130	-	+	+	+	+	D							
	150	-	+	+	+	+	D							
	125	-	+	+	+	+	D							

TABLE XIII  
SUMMARY SHOWING INFLUENCE UPON TRYPANOCIDAL ACTIVITY OF SHAKING  
ACID SOLUTIONS OF ARSPHENAMINE FOLLOWED BY ALKALINIZATION

PRODUCT OF LABORATORY	SMALLEST TRYPANOCIDAL DOSE PER KILO		
	ALKALINIZED AND INJECTED AT ONCE	SHAKEN ONE MINUTE AND ALKALINIZED	SHAKEN TEN MINUTES AND ALKALINIZED
T	0.004	0.002	0.006
U	0.004	0.004	0.004
R	0.004	0.002	0.004

TABLE XIV  
SUMMARY SHOWING INFLUENCE UPON TRYPANOCIDAL ACTIVITY OF SHAKING  
ALKALINIZED SOLUTIONS OF ARSPHENAMINE

PRODUCT OF LABORATORY	SMALLEST TRYPANOCIDAL DOSE PER KILO		
	INJECTED AT ONCE	SHAKEN ONE MINUTE	SHAKEN TEN MINUTES
T	0.004	0.002	less than 0.001
U	0.004	0.002	0.002
R	0.006	less than 0.002	0.006

TABLE XV  
SUMMARY SHOWING INFLUENCE UPON TRYPANOCIDAL ACTIVITY OF SHAKING  
SOLUTIONS OF NEOARSPHENAMINE

PRODUCT OF LABORATORY	SMALLEST TRYPANOCIDAL DOSE PER KILO		
	INJECTED AT ONCE	SHAKEN ONE MINUTE	SHAKEN TEN MINUTES
T	0.004	0.004	0.004 *
R	0.004	0.004	0.004 * *

\*Development of trypanosomiasis delayed to 17th day.

\*\*Development of trypanosomiasis delayed to 11th day.

to Toxicity, by George W. Raiziss and M. Falkov, *Jour. Biol. Chem.*, 1921, xlv, 209).

When arspenamine or neoarsphenamine is oxidized, the oxygen requirement becomes smaller, thus indicating quantitatively how much the drug has been oxidized. We found for a freshly prepared solution of arspenamine (Lot No. 5092) one gram required 123.5 milligrams of oxygen. After it was shaken vigorously for ten minutes, according to the method employed in the biological experiments reported in this paper, one gram required only 102 milligrams. We can see that the oxygen requirement decreased to the extent of 17.4 per cent. A fresh solution of neoarsphenamine (Lot No. 2090) required 103.7 milligrams of oxygen for one gram, and after shaking vigorously for ten minutes, required only 74 milligrams, indicating that the oxygen requirement decreased by 28.6 per cent. The same (Lot No. 5092) sample of arspenamine shaken only one minute required 114 milligrams of oxygen which shows a decrease in oxygen requirement of 7.69 per cent. The same sample of neoarsphenamine shaken vigorously for one minute, required 88.2 milligrams of oxygen, showing a decrease in oxygen requirement of 14.94 per cent. Neoarsphenamine (Lot No. 1937) originally required 112.1 milligrams of oxygen for one gram of the compound. After being shaken one minute, it required 102.5 milligrams. After being shaken ten minutes, it required 76.7 milligrams of oxygen, showing a decrease in oxygen requirement of 8.56 per cent and in ten minutes amounting to 31.58 per cent.

The above tests indicate the presence of arsenoxide in the experimentally shaken solutions of arspenamine.

#### COMMENT

A point of interest in connection with the above studies is the fact that after one minute's experimental shaking of acid and al-

kaline solutions of arsphenamine there is not only an increased toxicity of these solutions, but at the same time an increased trypanocidal effect. In other words a change in the drug has occurred which causes an enhanced poisonous effect both upon the body cells and upon the parasite.

Ehrlich and his associates pointed out the fact that slightly oxidized solutions of arsphenamine developed an increased toxicity by reason of the formation of "arsenoxide." Voegtlin and Smith<sup>4</sup> have made various studies and observations which have led them to believe that the trypanocidal and spirocheticidal action of arsphenamine is due to the formation of "arsenoxide" in the body after injection. They found that the sodium salt of arsphenamine which has been incubated at 37° C. for about three hours exerts a much greater trypanocidal effect than solutions that are freshly prepared. Furthermore after the injection of arsphenamine into rats experimentally infected with trypanosomiasis, the parasites begin to disappear from the blood only after a period of latency, whereas when a somewhat oxidized solution is injected the effect upon the parasites is immediate. They assume, therefore, that the blood or body tissues oxidize arsphenamine to "arsenoxide" and that in this form the drug exerts its real trypanocidal power. Whether this theory is correct or not, it has some apparent confirmation from the experiments which we report. As concerns the practical lessons to be drawn from the above studies, the following may be stated. Acid solutions of arsphenamine tolerate brief additional shaking without material increase in toxicity. Alkaline solutions are much more sensitive to oxidation upon shaking but agitation of alkaline solutions in practical work is rarely necessary. Roth's studies and our own both emphasize the importance of effecting solutions of neoarsphenamine with the least shaking possible, as additional shaking in the presence of air for even one minute materially increases the toxicity. Moreover, it is highly probable that long standing of neoarsphenamine solutions in contact with air or unnecessary pouring from one vessel to another would serve to act in a similar way.

#### CONCLUSIONS

1. The undue shaking of alkalinized solutions of arsphenamine increases the toxicity; the shaking of such solutions is rarely necessary.
2. The shaking of acid solutions of arsphenamine for one minute

beyond the time necessary to effect solution is accompanied by a slight increase in toxicity. Ten minutes' extra shaking increases the toxicity still further.

3. The shaking of solutions of neoarsphenamine for even such short periods as one minute is accompanied by a great increase in toxicity. Shaking for ten minutes enormously increases the toxicity.

4. It would appear from the studies of Roth and from those which we have conducted that neoarsphenamine should be dissolved with as little agitation and as little exposure to air as possible.

5. Different lots and brands of arsphenamine and neoarsphenamine vary considerably in their liability to oxidation on shaking.

6. The trypanocidal power of acid solutions of arsphenamine is considerably increased after one minute of shaking but is decreased after ten minutes' shaking.

7. The trypanocidal power of alkaline solutions of arsphenamine is considerably increased at the end of one minute's shaking and the increase is still evident after ten minutes' shaking.

8. The explanation of the increase in trypanocidal power is probably to be found in the formation of "arsenoxide," which is known to exert a greater trypanocidal and spirocheticidal effect than arsphenamine.

9. The shaking of solutions of neoarsphenamine is not accompanied by increase in trypanocidal effect.

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## PRACTICAL OBSERVATIONS ON SYPHILIS

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(Received for publication, January 18, 1922)

A SERIES of articles have been prepared at the special request of the publisher. Their object is to furnish both text and illustrations for the physicians who have not the opportunity of seeing a great deal of syphilis. In general, they follow the ideas set forth by the syphilologists who have lectured at the various Public Health Institutes. Every attempt has been made to give exhaustive comments in regard to the practical handling of the disease. The method of preparing the various drugs is dealt with at length, something that can be found in no textbook at the present time. In other words, this series of articles attempts to give practical aid to the general practitioner who is occasionally called upon to handle syphilis.

In order to save space bibliography is not included. This can be found in my book on "Syphilis." However, every physician should know where to turn to seek advice in regard to syphilitic problems. There are two short textbooks in English, these being by Loyd Thompson, published by Lea & Febiger, and by Hazen, published by the C. V. Mosby Co. Nonne has written an admirable book upon diseases of the Nervous System. This has been translated by Ball, and is published by Lippincott. The most important articles upon Syphilis appear in *The American Journal of Syphilis*, *The Archives of Dermatology and Syphilology*, and the *Journal of the American Medical Association*.

### Section 1

#### INTRODUCTION

Syphilis is the result of a chronic infection with the *Treponema pallidum*, and is characterized by more or less severe lesions in any portion of the body.

Within the past two decades our knowledge of syphilis has materially increased. The causal organism has been found and the dis-

ease reproduced with it; the Wassermann reaction, although not an unmixed blessing, has given great aid in diagnosis; arsphenamine has proved a most potent drug for treatment; and, last, a world wide campaign is being waged by governmental agencies.

#### HISTORY

Syphilis may or may not have existed in China and Japan between 1122 and 314 B.C. All authors agree that it was not until 1494, during the raid of Charles VIII upon Italy that the disease really attracted attention. In 1495 the army was forced to retreat and the troops who were mainly mercenaries from various countries, wandered back to their homes, spreading syphilis on the way. It is stated that the disease was much more *virulent* then than at present. The fact that syphilis first appeared in Europe after the return of Columbus lends plausibility to the theory that the disease was conveyed to Europe by the sailors of Columbus and this view is now generally held.

#### PREVALENCE

Statistical study as to the prevalence of syphilis can be conveniently found in Vedder's book on "Syphilis and Public Health." Unfortunately, it is difficult to say just what per cent of the population is affected because the incidence of the disease is different in different groups of the population. Many of the figures are unreliable because there has been a tendency upon the part of too many observers to make a positive diagnosis of syphilis upon a single positive Wassermann.

Various figures from Germany as quoted by Vedder would seem to show that about 20 per cent of German men are infected. Fournier estimated that 15 per cent of the adult population of Paris are infected with syphilis.

In the United States certain groups have been studied. It is safe to assume that practically all professional prostitutes suffer from syphilis. Among the insane the figures run from 12 to 20 per cent of positive findings. Among the hospital class from 10 to 20 per cent of all patients show signs of the disease. Among the cadets at West Point 5.5 per cent were found to be infected. It is generally estimated that there is twice as much syphilis in the negro race as in the white, but that there is one very important difference; namely, that the disease is just as frequent in the negro

female as in the negro male, while in the white race it is probably three times as frequent in men as in women.

The probabilities are that there are between five and eight million syphilitic individuals in the United States.

#### ECONOMIC IMPORTANCE

Unfortunately there are very few articles that deal with this aspect of syphilis. Leredde has estimated that syphilis causes 25,000 deaths a year in France, and my own figures for the United States are very similar. Of course, the vast majority of these deaths come from central nervous system, cardiac or vascular types of the disease. Reports from the American Life Insurance Companies show that the mortality among those who have a history of the disease is  $33\frac{1}{3}$  per cent above expectations.

In addition syphilitic women do not bear the number of living children that they otherwise would. A very high percentage of miscarriages is directly attributed to syphilis, so are many of the early deaths among the newborn. In addition to the loss of life, it must be remembered that much time is lost from useful occupation and much money is spent in doctors' and druggists' bills. The cost of caring for the syphilitic insane reaches very high figures. Stokes has estimated that the actual monetary loss is about five billion dollars a year. He has shown that syphilitic insanity alone costs one-tenth of this figure.

## Section 2

#### ETIOLOGY

As Osler well remarks "the story of the search for the cause of syphilis is a tale to make the judicious grieve." In 1905 Lassar stated: "One hundred and twenty-five causes of syphilis have been established during the last twenty-five years." The earlier history as to its relationship to gonorrhea and chancre is not particularly elevating. John Hunter, the great physiologist and surgeon, as the result of an experiment, whereby he inoculated himself with supposedly gonorrhea pus and later developed syphilis, taught that there were three kinds of venereal infection, gonorrhea, chancre, and lues venerea, and that all were the result of the same poison, the only difference being the nature of the surface upon which the virus acted. Bell, both as the result of experimental work and of



clinical observation, could not accept these doctrines and consistently fought against them. Ricord in 1838 made the first impression as to the differences between syphilis and gonorrhea. Ricord's pupils, Bassereau, Clere, and Fournier clearly showed that syphilis and chancroid were two distinct affections.

The protozoologist, Fritz Schaudinn, and syphilologist, Erich Hoffmann, first demonstrated the presence of spirilla in a condyloma on March 3, 1905. The publication of the first reports led to an immense amount of work, and the discovery was speedily verified from many sources. The organism was at first called the *Spirocheta pallida* but is now known as the *Treponema pallidum*. Nichols compares the appearance of the organism to that of a spirally wound wire. It is from four to fourteen microns in length and has a thickness of about one-quarter of a micron, and contains from six to fourteen spirals, which are close set and regular. Occasionally larger specimens with more windings are found. No internal structure can be demonstrated. The parasite is extremely motile, and there is a considerable amount of lateral flexibility.

As yet we know practically nothing concerning the life history of the organism. McDonagh believes that the form that we know is simply the male gamete of a sporozoan parasite, and that the other forms can be demonstrated in the lymph glands by means of a pyronin and methyl green stain, and *in vivo* with borax methylene blue. However, his work has not found general acceptance, largely because of the fact that the treponema can be cultivated for hundreds of generations and only one form found.

The treponema is present in large numbers in the primary and secondary lesions, and has even been demonstrated in the brains of paretics. During the acute stage it can be found in the blood and in various of the secretions of the body, although not in large numbers.

The organism of syphilis quickly becomes sluggish after being removed from living tissue. Postmortem material is infectious at the end of twenty-four hours, and treponema may survive in tissue at room temperature for seventy-two hours. Drying promptly kills them. They are killed fairly early by most antiseptics, and it is a matter of great importance that soap and water proved almost immediately fatal.

Akatsu has found that he can cause the resistance of trepon-

emata to be raised to the mercurials, and also to some extent to arsphenamine by growing the organism in a culture containing traces of these substances.

#### INFECTION

Syphilis may be either congenital or acquired. The mechanism of the former is imperfectly understood. There can be no question but that the vast majority of the cases are of maternal origin, the organism gaining entrance to the child through the placental circulation. The question of paternal transmission is a most important practical one, and at the present time is not fully settled. Certain recent observations may show that this mode of infection is possible.

The majority of cases are acquired. Of these acquired cases about 94 per cent have the initial lesion upon the genitals, the infection being the result of sexual intercourse. In the remaining 6 per cent the primary lesion is situated upon some other portion of the skin or mucous membrane; these lesions constitute the extragenital chancres. However, such chancres are by no means always innocently acquired, for they may arise as the direct result of perverted sexual habits. The commonest of the extragenital lesions is one of the lip, and this usually results from kissing someone with a mucous patch. Schamberg's report of an epidemic of such chancres is noteworthy as showing the extreme contagiousness of these chancres. In Schamberg's cases the primary source of infection was a young man with a labial chancre. "Six young women kissed by him developed chancres of the lip. A young man present at the affair likewise developed a chancre of the lip apparently from the virus deposited on the lips of one of the women, for he did not come in contact with the original source. In addition a young woman kissed by the offender at a third social function likewise developed an initial sclerosis, making in all eight labial chancres from the one source." Later Schamberg was consulted by another girl who had acquired a chancre of the cheek from one of the young women previously mentioned.

Bulkley has written a very entertaining little book upon the subject of innocently acquired chancres. In addition there are many cases recorded in the literature. One of the commonest sources of extragenital infection is kissing, as has already been indicated. Next in frequency undoubtedly ranks professional in-

fection, where a physician becomes contaminated as the result of handling a syphilitic sore. The following classification is modified from that in an article by Bulkley:

### I. Immediate Contact.

1. Sexual contact may give rise to chancres upon the thighs or abdomen.

2. Perverted sexual habits may cause chancres of the mouth, anus or breast.

3. Kissing may cause chancres of the mouth or face.

4. Biting occasionally gives rise to chancres. Policemen have been infected by being bitten while making an arrest. I know of one instance where a young man struck a prostitute in the mouth, cut his hand by so doing, and developed a chancre at the seat of the injury.

5. Suckling children with congenital syphilis give rise to many initial scleroses in wet nurses. The practice of drawing the nipples has also caused many chancres of the breasts.

6. Some babes have been infected at birth as the result of coming in contact with fresh lesions upon the genitals of their mothers.

7. Instances of infection from sleeping with an infected individual are authenticated.

8. Physicians, nurses, medical students, and midwives have only too frequently been inoculated while in the discharge of their professional duties.

9. Children have been infected by being cared for by syphilitic nurses.

### II. Mediate Contact.

1. Syphilis is occasionally acquired from infected eating and drinking vessels. This cannot be a common means, for cases are but rarely reported. In Russia the use of a common spoon by the peasants is the cause of many cases.

2. The use of infected water closet seats must be a very rare cause, although it is one frequently alleged by patients.

3. The use of infected towels, napkins, handkerchiefs, etc., may cause some infections. I have had one case that undoubtedly came from handling the towels of an active syphilitic.

4. Children may be infected by nursing bottles, diapers, etc. It

is rather surprising that more cases are not recorded in the hospital wards.

5. The passing of vaginal syringes from one woman to another has caused a number of chancres. Likewise many cases have been reported from glass work, where one workman would infect a blow-pipe and another would use it. The use of infected pipes, and even of cigars and cigarettes has caused some cases.

6. Formerly there were many cases as the result of vaccination, but now that calf lymph is used there are practically no cases reported, except where the physician is responsible or where the wound is later infected. The practice of tattooing has caused more chancres than would be supposed. Ritual circumcision has likewise been responsible for many an infection. When it was the practice to bleed most patients, and sterilization was unknown, many initial scleroses were induced in that way.

7. As the result of minor operations, dressings, etc., some few cases of syphilis have been caused. I have seen one chancre of the foot which developed while the patient was in a hospital for a long time.

8. The use of infected dental instruments has resulted in more than one case of mouth infection.

9. Infected eustachian catheters have caused quite a number of infections.

10. Infected razors have caused some chancres of the face.

So far there are very few cases upon record where syphilis has been transmitted from one person to another by an insect carrier, but the possibility should always be borne in mind.

It is usually estimated that about 20 per cent of syphilitic infections are innocently acquired, that is, not as the result of illicit sexual intercourse. Only too frequently wives are infected by their husbands. Undoubtedly the condylomata that often linger so long about the genitals give rise to more syphilitic infections than any other type of lesion, for they simply swarm with organisms.

It is a bit uncertain how long an infected individual is dangerous to his associates. All are agreed that the disease is very contagious during the primary and secondary stages, while there is considerable doubt as to the power of an infected individual to infect any one after he has had the disease for more than four years. However, I am certain that I know of at least two instances where

a syphilitic infected his partner over twenty years after the date of his initial lesion. The proof that treponemata are present even in as late lesions as paresis should serve to make one very cautious in asserting that the danger period soon passes.

A break in the skin or mucous membrane is usually considered to be necessary in order that the treponema may gain entrance to the body. Such minute breaks are very common during sexual intercourse.

Cases have been reported where surgical assistants have punctured the skin with an infected instrument, and while under close observation developed generalized syphilis without an initial lesion.

It has been rather generally believed that a patient suffering from syphilis could not be reinfected, but recent experimental work would seem to conclude that a small amount of treatment may so change a patient's resistance that a second infection is possible even though the first infection has not been cured. Thus we can no longer hold the presence of a new infection as a criterion for a cure of the original infection.

Another question of extreme importance is that of strains of the treponema. The experiment of Nichols and of Reasoner would seem to show that there exist various strains of the infectious organism which have an affinity for certain tissues. For instance, it has been believed that syphilis of the nervous system is due to an infection with a breed of treponema which has a special affinity for nerve tissue. The important observation of White that patients suffering from cerebral syphilis have but rarely shown cutaneous manifestations gives a certain amount of clinical corroboration to the experimental work. In addition, it is well known that persons infected from the same source not infrequently develop lesions of the same general type. Years ago Osler taught his students that the presence of cerebral syphilis was common in both husband and wife.

Brown and Louise Pearce are at present engaged in elaborate studies of infection, and the results of these studies are being published in the *Journal of Experimental Medicine*, *The Archives of Dermatology and Syphilis*, and *The American Journal of Syphilis*. Every one who is interested should read these papers. In addition, from Engman's clinic there has appeared an important article showing that the seminal fluid from a long standing case is occasionally actively infectious.

## IMMUNITY

At the present time we know very little concerning immunity in syphilis. There is abundant clinical evidence to show that the body possesses some natural resistance towards the *Treponema pallidum*, but concerning the nature of the immune body we are almost completely ignorant. Culture organisms are agglutinated by the sera of rabbits, *treated* with culture organisms, and recent work would seem to show that the blood of treated patients likewise contains agglutinins. An important practical question is whether or not mercury acts by building up the resistance of the body, rather than by killing the organisms.

Racial immunity does not exist despite some claims to the contrary.

The expression "Latent syphilis" is a much abused one. As ordinarily employed it simply means that no active syphilitic lesions are in evidence to the eye; only too frequently during a so-called latent period the central nervous system or the aorta is suffering.

## GENERAL PATHOLOGY

After the treponema is implanted, it begins to multiply, to call forth changes in the cutaneous vessels, and to enter the blood and lymph streams.

Within three days the organism can be demonstrated in the satellite lymph nodes, and very shortly thereafter in the spleen, bone marrow, and other lymph nodes. This is an excellent argument against excising the chancre as a routine therapeutic measure.

As the chancre develops, a peculiar reaction upon the part of the body is also forming. At first it is so feeble that the patient is liable to reinoculation. In animals it has been found that superinfection is possible if made within eight days before the evolution of the primary sclerosis. Multiple chancres in the human being may result from multiple simultaneous inoculations, from autoinoculation, or from a separate and later inoculation.

It is well known that the first or initial lesion is usually solitary, but that during its development the treponemata are actively engaged in multiplying in various portions of the body as mentioned above. Then there occurs a sudden dissemination of them, a septicemia as it were, which is *generally* held to be limited to the superficial structures of the body, notably the skin and mucous sur-

faces. In the due course of time, just how long is still unknown, their presence calls forth a reaction on the part of the tissues in which they are lodged, and this reaction is best known in the form of the secondary syphilides of the skin and of the throat and mouth. However, it is becoming more and more certain that at this time many of the deeper structures are invaded. As an example of this it is only necessary to call attention to the recent work showing that the central nervous system is involved in a high percentage of cases at this early date. Fortunately the resulting lesions, which must be considered as the expression of tissue reaction to the treponema, are usually comparatively mild in character and do not result in the destruction of tissue.

During the course of late syphilis the lesions are localized, are fewer in number, and there are fewer organisms present, but ulceration usually results. This difference upon the part of the bodily reaction is not believed to be due to a change upon the part of the organism, but to a change in the tissues of the body to which the term "allergy" is applied. In the early stages where the organisms are numerous the host is refractive, but in the later stages when the organisms are comparatively few in number the tissues are more susceptible and readily undergo necrosis. The so-called malignant syphilis is simply due to an early allergy upon the part of the body of the victim.

These processes of immunity are subject to modification under treatment. Where treatment is intensive and yet not sufficient to complete a cure, the anaphylactic stage may be hastened, and specific treatment given early in the course of the disease may tend to produce relapses of increased local intensity. In this connection we may note that it is claimed by some that the use of arsphenamine has changed the course of the disease, and that when it is not given in sufficient quantity to sterilize the patient, tertiary lesions may appear much earlier than when the disease is permitted to run its natural course with the production of a natural defensive mechanism.

The relationship of trauma to syphilitic lesions is now pretty generally recognized. The query arises whether the organism was present at the site of injury or was later deposited at that site. As bearing upon this point Pasini has demonstrated treponemata in an atrophic and pigmented spot two years after the involution

of a papular syphilide, while Hoffmann had demonstrated them in a scar of a chancre long after the disappearance of the primary focus. The so-called chancre redux or relapsing chancre is interpreted by many as being the result of organisms which have remained *in situ*, rather than as a superinfection. Neisser has shown that the organisms may be present in the skin without calling forth any tissue inflammation.

Studies upon the infectiousness of the blood by Uhlenhuth and Mulzer have supplied us with the following data:

PRIMARY STAGE			SECONDARY STAGE			LATE STAGE		
No.	Cases	Positive	No.	Cases	Positive	No.	Cases	Positive
19		16	36		27	15		2

The above facts are in accord with clinical observations that the blood of luetic individuals is infectious during the primary and secondary stages, but that this infectiousness decreases as the disease becomes older. Kraus has suggested that the febrile attacks that sometimes accompany syphilis may be due to a sudden dissemination of the treponemata, an analogy being found in leprosy or trypanosomiasis.

Fordyce's article contains an elaboration of the above views, and it is to this article that I am much indebted.

Syphilis has certain general effects upon the general system. As is well known the number of the red blood cells and the amount of hemoglobin is sometimes decreased. In the European clinics considerable stress was formerly placed upon this fact as a diagnostic sign, particularly in women. In America there does not seem to be so general an anemia, but nevertheless it does often occur. The administration of mercury to a syphilitic frequently causes a marked drop in the quantity of the hemoglobin, and this was considered by Justus to be characteristic of the disease. I have definitely shown that an increase in the number of leucocytes not infrequently accompanies the early and sometimes the late stages of the disease. The administration of either mercury or arsphenamine causes a rise in the actual and relative number of the small mononuclear cells, although the same is true of nonsyphilitic subjects.

As a general rule there is very little evidence of kidney irritation, although at times there may be a trace of albumin in the urine. A true nephritis is usually due to either the administration of mer-



cury, to a true gummous formation, or more rarely to amyloid degeneration.

The flow of gastric juice is sometimes markedly altered during the florid stage, and it is not unusual to find acute but temporary gastric disturbances during this period. This may be due to an eruption upon the mucous membrane, a true gastritis, or to a disturbance in the quantity of the secretions.

#### HISTOLOGIC PATHOLOGY

Fordyce pertinently remarks: "The predilection of syphilis for the vascular system is noted almost from the inception of the disease in the involvement of the cutaneous vessels at the point of inoculation. Here the pathologic process consists of an endarteritis, later a periarteritis with characteristic inflammatory infiltration \* \* \* A Study of the pathologic anatomy of syphilis shows that fundamentally the reaction is on the part of the connective tissue elements, the labile constituents coming into play only secondarily. The chief cells are the lymphocytes and plasma cell, the latter believed to be a derivative of the former and an antecedent of the fibroblast". No matter at what stage a syphilitic reaction develops, it is essentially a granuloma having its origin in the perivascular lymph stages. This is true of all forms and of all stages of syphilis, with one exception, namely, the primary syphilis of the heart muscles, as will be pointed out in the section devoted to that organ.

In the secondary lesions the lesions are very similar to those just described, except that a massive infiltration is rare; the infiltration while heavy, can usually be seen to surround blood vessels. In general the vessels are thickened and the endothelium swollen and proliferated. A panarteritis is common. Giant cells are more common than in chancre, but are none too frequently encountered.

In the late lesions there are two distinct types of involvement. With the exception of the heart muscle the involvement is always interstitial and always begins around the blood vessels. This is especially noticeable in the various glandular organs and also in the lungs. While the beginning is the same, the later course of the two processes is markedly different. In one type there is the formation of numerous miliary gummata that run in bands along the interstitial tissue and which never completely necrose,

but which are soon replaced by scar tissue, and at times eventually by calcareous deposits. This is the type that gives rise to the cirrhosis of the various organs. In the other type one or more frank gummata form. These begin just as do the other syphilitic processes, but the tissues are friable and necrosis follows at some later date, sometimes within two weeks and sometimes not for nearly two years. The gummata are large and the ulcerative processes always seek the path of least resistance and eventually ulcerate to the surface or into some bodily cavity.

Recently Warthin has written a very interesting paper which should be read by any one interested in the pathology of syphilis. Warthin points out that microscopically the inflammation of syphilis is characteristic, and that the condition can frequently be recognized only microscopically, certainly not by the naked eye. In many instances there is but a mild degree of the characteristic perivascular infiltrate, not sufficient to call a granuloma, and yet the treponema can frequently be recognized by the Levaditi stain.

#### AUTOPSY FINDINGS IN SYPHILIS

From a study of the gross anatomy Symmers found in a study of 4,880 autopsies performed at the Bellevue Hospital evidence of syphilis in only 314 cases, or 6.5 per cent. Lesions of the skin were found 106 times, hyperplasia of the lymph nodes 20 times, bone lesions 48 times, orchitis 67 instances, lesions of the respiratory tract 35 times, lesions of nervous system in 112 cases, syphilis of the liver 105 times, aortitis in 175 cases, aneurysms in 45 cases, gastric ulcer once, and the intestines were involved six times.

In marked contrast to these findings are those of Warthin, who also made a careful histologic examination of all tissues, and he reports that in 750 autopsies performed at Ann Arbor during the last ten years evidence of syphilitic infection was found in no fewer than 300 cases. Warthin points out that the gross anatomic study as done at the autopsy table will not establish the diagnosis of syphilis in the majority of cases, a view with which I most heartily coincide.

Recently Graves has extended his original report of the postmortem Wassermanns and has found that the postmortem reports confirmed the antemortem reports in 97 per cent of the cases. This may be of value in medicolegal cases.

### Section 3

#### CLINICAL COURSE

In the past it was customary to divide the course of syphilis into four stages. The primary, which includes the chancre and the enlargement of the nearest chain of lymph nodes; the secondary, which covers the stage of generalization; the tertiary, which covers the appearance of gummata in various portions of the body; the quaternary, or parasyphilitic, which includes tabes and paresis. At the present time, however, the tendency is to make but two stages, the early stage, which covers the first six months, and the late stage, which begins with the disappearance of the lesions induced by the septicemia.

The incubation period varies from three to six weeks, with an average of four.

The primary lesion is known as the chancre, and may appear upon any portion of the skin or mucous membranes, although usually upon the genitals. In exceptional instances no chancre is seen. However, as a general rule, close examination will reveal the presence of a lesion in an obscure location, as in the urethra or upon the cervix. At times, too, the initial lesion may be so small and insignificant as to escape notice. When there is no chancre the condition is spoken of as "syphilis d'emblee" and has been carefully considered by both Almkvist and Gottheil, both of whom consider it extremely rare. The former believes that there are only four cases upon record, those of Jullien, Waelsch and Bettmann, which are conclusive. All four of them occurred in physicians who cut or pricked themselves during an operation. Since this time both Fordyce and I have recorded similar cases in which there could be no doubt. In addition to these the literature contains about twenty-five cases in which no initial lesion was found.

In addition to the chancre the primary stage also includes the local lymph node involvement, which is usually quite evident. Ordinarily this develops in from two to three weeks after the appearance of the initial sore. The glands in connection with an extra-genital chancre are usually much larger than those from a genital one.

In the preceding chapters I have called attention to the fact that it has been shown by Neisser that the *treponemata* can be found

in various lymphatic structures by the time that the chancre has manifested itself. As a general rule during the periods of incubation and of subsequent development of the chancre there is but little general disturbance. However, at times even for several weeks before the chancre appears there may be systemic disturbances. Recently I saw a physician for a chancre of the finger, who had lost over twenty pounds in weight and who had felt very ill for a month before the initial sclerosis manifested itself. I have seen several other cases in which the general health suffered greatly while the chancre was present and before the rash appeared. These disturbances consist of malaise, loss of weight and strength, and general lassitude.

#### THE EARLY STAGE

The secondary or early stage is due to the widespread dissemination of the organisms, a septicemia, with most of the lesions superficially located in either the skin or mucous membranes. This stage usually appears in from four to twelve weeks after the initial lesion has first manifested itself. Its most prominent characteristic is usually the rash, which may assume any one of many forms. In addition there is often a pharyngitis and the so-called mucous patches of the mouth and lips, which are simply modified papules. Condylomata or moist papules may appear early, but usually do not erupt for several months. Some degree of alopecia occurs in about 10 per cent of all secondary cases. Arthritic pains occur in a large percentage of all patients. Headaches are common, and may denote early involvement of the central nervous system, or may be simply signs of a general toxemia. A more or less general glandular enlargement occurs in about 50 per cent of the whites, but in a much higher proportion of negroes. Iritis is not infrequent. In addition there are frequently certain general disturbances. A moderate amount of fever is found in many cases, especially in patients with pustular lesions. Bronchitis is frequent and laryngitis not uncommon. Some patients show marked digestive disturbances, and I have seen cases in which there was persistent vomiting for weeks. Acute yellow atrophy of the liver has been reported by many observers, and some jaundice is not infrequently seen. The spleen is often enlarged. There is at times some anemia, usually of the secondary type, and the leucocytes are

often increased. However, the lesions may be ulcerative or gum-mous from the first, due to the resistance of the patient and not to any special virulence on the part of the treponema. As a general rule the early manifestations disappear even if untreated, but both the mucous patches and the condylomata are often very stubborn. In White's series of 505 secondary cases cutaneous manifestations were seen in 225 patients, mucous patches in 226, pharyngitis in 193, iritis in 25, condylomata in 41, headache in 133, and alopecia in 47.

Following the secondaries there is often a so-called latent stage of varied duration, sometimes two months and sometimes ten or even more years, but usually about two or three years, before the deeper lesions begin to appear. The stage is called the early latent period. In many instances before the appearance of the late lesions there may be a recrudescence of the secondaries, either mild or severe. Such a recurrence undoubtedly takes place in at least 20 per cent of all syphilitics who neglect treatment. Mucous patches and condylomata are especially apt to develop during this period, and various varieties of superficial cutaneous rashes are far from rare. Associated with such outbreaks there may be any of the other signs of syphilis already mentioned, and in addition some deeper lesions are not uncommon.

#### THE LATE STAGE

The tertiary or late stage consists of gum-mous processes, unusually localized to some particular organ, although many may be affected at one time. Either deep or superficial structures may be attacked, but the treponema has a marked predilection for nervous and arterial tissues, bone, skin, liver, testicles and adrenals. Any organ, without exception, may be invaded. This stage rarely appears in less than eighteen months after the appearance of the initial lesion, and may be delayed for even a score or more years. There are but few organisms present, so it is evident that the accompanying necrosis is due to a state of allergy upon the part of the tissues. When the lesions are visceral there is apt to be intermittent fever, but this is by no means always the case.

Following the definite gum-mous manifestations there is usually a so-called latent period of varying lengths, during which time there are no evident lesions, but during which time either the

nervous, arterial or some other structures may slowly become involved. This period may be interrupted at any time by the formation of gummata. This late, apparently quiescent, period may continue indefinitely, sometimes for thirty or even more years, without there being evident clinical manifestations. It should always be remembered that syphilitic changes in concealed organs only too frequently develop during this time.

The quaternary, or parasymphilitic processes, namely, paresis and tabes, are true syphilitic processes as has been abundantly proved.

Malignant syphilis deserves special consideration. In this type the ulcerative processes begin at a very early date, due to allergy on the part of the host. The disease usually starts in the characteristic way, but the papules ulcerate deeply and rupial crusts cover the ulcers, which are often very numerous, but fortunately confined to the skin or superficial mucous surfaces. There is usually cachexia and emaciation, and death from asthenia may supervene. In some instances even the chancre may assume an ulcerating aspect, but this is not usual. In other instances an apparently benign case may later assume a most malignant form.

During the secondary stage a small percentage of cases show some fever, and this may be intermittent, remittent, continuous, or irregular. The fever of the late period is most interesting for it may be severe and of long duration, and may simulate typhoid, malaria, or occasionally tuberculosis or a septic process. It seems especially apt to be associated with hepatic syphilis, or more rarely with meningitis.

## Section 4

### THE CHANCRE

As already stated the chancre is to be considered as the earliest reaction upon the part of the body to the *Treponema pallidum*. In about 94 per cent of the cases the initial lesion is present on the genitalia. In the remaining cases it is extragenital in locality.

Chancres can be conveniently divided into three groups. First, the genital chancre in the male; second, the genital chancre in the female; and third, the extragenital chancre.

In the male the chancre is most apt to be located in the coronal sulcus, next in frequency it develops in one of the small fossae upon either side of the frenum. However, it may develop upon

the glans, upon the body of the penis, or even within the urethra. Entirely too many clinical types have been described for all are really stages of one process. It is common to state that there are three chief varieties: the erosive, the ulcerative, and the papular. All have certain characteristics in common: in the first place they are usually painless, but itch a trifle; in the second place they are usually indurated, both beneath and at the edges: the top is usually raw and exudes a serous fluid; they are usually single, but in

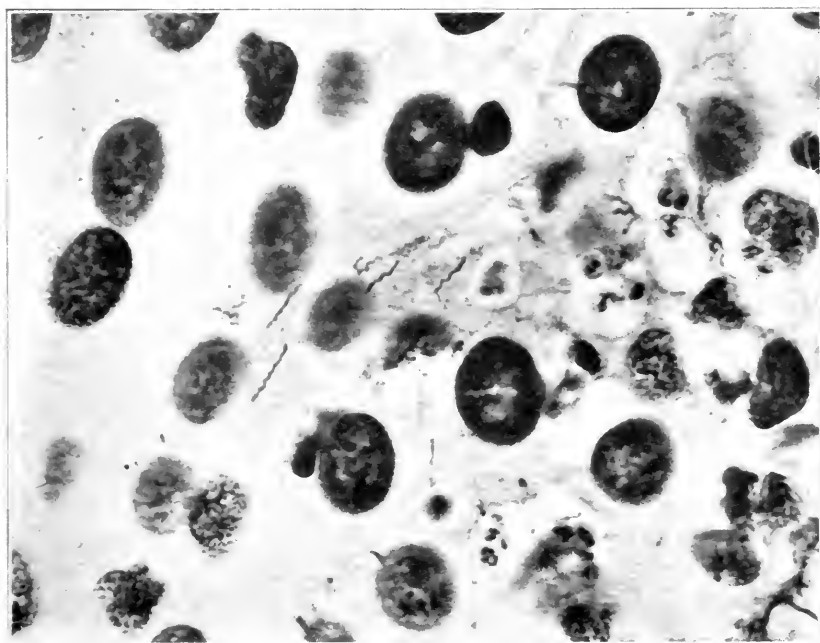


Fig. 1.—This section from the wall of a hair follicle in secondary syphilis shows well the structure of the *Treponema pallidum*. (Courtesy of Dr. C. C. Dennie.)

nearly 10 per cent of the cases may be multiple. In diameter they vary from three millimeters to nearly two centimeters. A point that cannot be too strongly emphasized is that a chancre may be absolutely atypical, and that it may last but a day or two. *Every syphilologist believes that absolutely every genital abrasion or sore should be suspected as syphilitic until proved otherwise. The diagnosis of genital chancre should be made through laboratory and not through clinical evidence.* The dark-field illuminator is a proper

means for this diagnosis and any physician who fails to have patients examined by this method is guilty of moral malpractice.

In women about one-half of the lesions occur upon the *labial* majora, and the majority of the others either upon the *labial* minora or the fourchette. The cervix is occasionally the seat, but only rarely are the vaginal walls affected, although a German con-

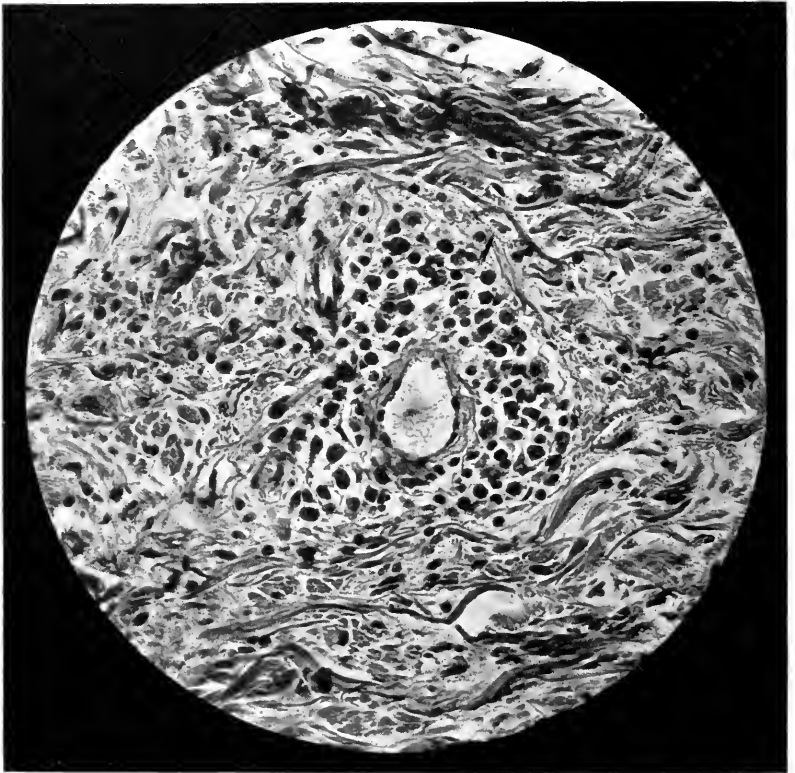


Fig. 2.—This illustration shows the perivascular infiltration occurring in a secondary skin lesion. The plasma cells show very distinctly. (Collection of Drs. Fordyce and MacKee.)

frere, who may need a spinal puncture done upon himself, has reported 21 instances.

Extragenital chancres are apt to be larger than the genital ones; they are usually ulcerative and are covered with brownish crusts, they are frequently 2 or 3 centimeters in diameter, and often markedly resemble a rolled-edge basal-celled cancer. The lip is



far and away the most frequent site for such lesions; next in frequency come the finger, particularly of physicians and more especially of obstetricians and laryngologists, the tonsil, the glabrous skin, and the tongue. Chancres at the mouth of the eustachian tube, those resulting from vaccination or from blood-letting, and lastly those of the breast in wet nurses, although formerly seen, are now extremely rare.



Fig. 3.—Chancres of the coronal sulcus with an indurated edge are absolutely typical; there is no other lesion that resembles them. (Collection of Drs. Fordyce and MacKee.)



Fig. 4.—In labial chancres the rim may be raised and hard. (Collection of Dr. Richard L. Sutton.)

The rapidity with which all of these lesions develop, the rapid enlargement of the draining lymph nodes, as well as the fact of their resistance to external medication, will serve to differentiate them from cancer. The finding of the *Treponema pallidum* by dark-field examination is confirmatory, and most *important*. It is



Fig. 5.—Chancres of the tongue are similar to those of other mucous membranes. (Collection of Drs. Fordyce and MacKee.)



Fig. 6.—Chancres of the glabrous skin are frequently large in size. (Collection of Dr. T. Caspar Gilchrist.)

a very curious fact that at least one-third of the cases of extra-genital chancre which I have seen, have been diagnosed as tuberculosis; no law of God or man can excuse such an error.



Fig. 7.—Chancres of the fingers are not rarities in the medical profession. In this instance the infection was acquired in examining for adenoids with an ungloved finger.



Fig. 8.—Chancres of the foot are very rare. This typical lesion was acquired in an unknown way during a stay in a hospital.

### Section 5

A new classification for the eruptions of acquired syphilis has recently been suggested by George Henry Fox, and adopted by the American Dermatologic Association. I shall use it, with two slight additions.



Fig. 9.



Fig. 10.

Fig. 9.—Macular syphilides are pale and difficult to photograph. This patient also has a chancre of the chin. (Gilchrist's case.)

Fig. 10.—Syphilitic leucoderma usually affects the necks of women. (Collection of Dr. Richard L. Sutton.)



Fig. 12.—Miliary or follicular syphilides are more common in negroes than in whites. This patient also had broken-down syphilitic glands of the neck.



Fig. 11.—A maculopapular syphilide may closely resemble urticaria.



Fig. 13.



Fig. 14.

Fig. 13.—The lenticular syphilides stand well up above the level of the skin.

Fig. 14.—Frambesiform or hypertrophic syphilides are rather unusual.



Fig. 16. In this instance the large discoid papules were sharply localized.



Fig. 15. The discoid syphilides are almost characteristic.

The ordinary macular syphilis is probably the commonest form of secondary syphilis in the whites. These roseolar spots may be either large or small, with all transitional stages. They may be so



Fig. 17.—Annular lesions are most frequent around the mouth. (Collection of Dr. T. Caspar Gilchrist.)



Fig. 18.—Discoid, squamous lesions may resemble psoriasis. (Collection of Dr. Robert G. Washburn.)

faint in color that it requires an excellent light to see them, or they may be a dark purplish-red. The small ones are apt to be light in color, and the large ones of a darker color. They are usually more



## EARLY

FORMS	VARIETIES	DESCRIPTIVE ADJECTIVES
Macular .....	Roseolar .....	Large, small.
	Annular .....	
	Vitiligoid .....	
Maculopapular ...		Wheal-like, annular.
Papular .....	Miliary .....	Disseminate, corymbose, annular.
	Lenticular ....	Disseminate, corymbose, annular, hypertrophic, confluent, squamous.
	Discoid .....	Disseminated, moist, annular, confluent, squamous.
Papulopustular ...		
Pustular .....	Acuminata ....	Crustaceous.
	Obtuse .....	Crustaceous.
	Ecthymoid ....	Crustaceous rupial, ulcerative.

## LATE

FORMS	VARIETIES	DESCRIPTIVE ADJECTIVES
Nodular .....	Agminate .....	Confluent, squamous, cicatricial.
	Circinate .....	Squamous, crustaceous, ulcerative.
	Serpiginous ...	Crustaceous, ulcerative, cicatricial.
Squamous .....	Diffuse .....	
	Circinate .....	
Gummous .....	Diffuse .....	Verrucous, crustaceous, rupial, ulcerative.
	Tuberous .....	Ulcerative, cicatricial.



Fig. 19.—Condylomata are simply moist discoid papules.



Fig. 20.—The pustular syphilides may be extremely superficial.



Fig. 21.—In this instance an agminate nodular lesion resembled a cancer; diagnosis was rendered more difficult by a negative Wassermann.

prevalent upon the trunk and limbs than upon the face. As a general rule they give no subjective disturbances.

The annular syphilides of a macular character must be sharply divided into two kinds, the instances where macular lesions become

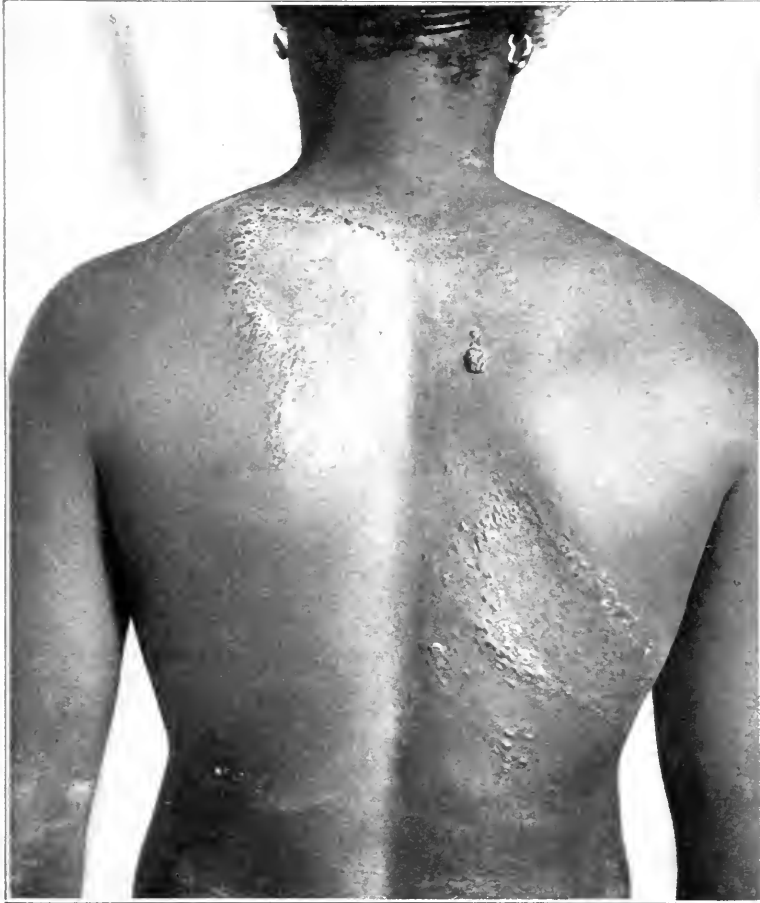


Fig. 22.—Serpiginous nodular syphilis is characteristic. (Collection of Drs. Fordyce and MacKee.)

annular, and the erythema multiforme-like lesions, the “neurosyphilides” of Unna. The former are simply modifications of the roseolar lesions, but the latter are more apt to come on after the infection has existed for several years, to be sharply limited to a small

portion of the cutaneous surface, and not to show the characteristic histopathology of syphilides. Unna believes that they are due to nerve lesions.

The vitiligoid lesions develop upon the neck, nearly always in women. There are present whitish macules, surrounded by a pigmented area. Some have thought that they represent faded syphilitic spots, but this is apparently not always true. They vary from one to four centimeters in diameter, are not very well defined, and last for a considerable time.



Fig. 23.—Broken-down gummata may be multiple; the leg is a common site.

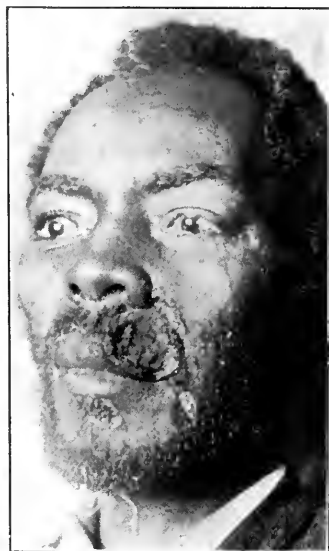


Fig. 24.—Solitary gummata are usually larger than are multiple ones. Note a ringed lesion just beneath the lip.

The maculo-papular lesions are of two varieties, the ordinary wheal-like lesions, and the annular ones. The former chiefly affect the trunk and limbs. They are rather a pale pinkish color, and are usually oval in shape, well defined, and about one centimeter in length. They closely resemble the wheals of urticaria. The annular lesions are simply modifications of these, and occur chiefly in the negro.



Fig. 25.—Rupial crusts are not especially common. (Collection of Dr. Robert G. Washburn.)



Fig. 26.—Diffuse subcutaneous infiltrations frequently end in localized ulcerations.



Fig. 27.—Early palmar syphilides are prone to develop in the lines.



Fig. 28.—Usually in palmar syphilides the skin at the edges curls up and there are fine scales.

The miliary papular lesions are seated at the mouths of the hair follicles. They are rare in whites, but not infrequent in negroes. The individual lesions are widespread, although the face is often

spared. The lesions are conical in shape, and vary in diameter from one to three millimeters. There is a tendency for the lesions to be grouped, although this is by no means always true.

When corymbose there is usually lacking the central "bull's eye," and the lesions simply form a large circle.

The annular lesions are of two kinds, first where one papule spreads peripherally and clears up in the center, and secondly where a number of follicular papules form a ring.

The term "lenticular" means a solid raised lesion, either acuminate, rounded or semiglobular. They are quite distinct from the discoid lesions, which are flat.

These lenticular papules are often widely disseminated over the entire body, the face not being spared. They vary in size from four millimeters to a centimeter, or even more. In color they are either a pale or fairly deep red, and often they have a few central scales. They tend to form in groups, and not to be absolutely evenly distributed.

When corymbose there is one large central papule, or bull's eye, around which are closely grouped many smaller lesions, sometimes so closely as to form a solid mass. These lesions are rather rare.

Lenticular papules occasionally become annular, at least in the negro, although not so commonly as the discoid or flat papules. The center may clear up entirely as the peripheral spreading takes place, or it may simply sink and become covered by thick whitish scales.

Hypertrophic rounded tumors, or large frambesiform lesions may develop from these lenticular lesions. Usually they are upon the face, but they may also occur around the genitalia, in the axillæ or around the breasts. Very rarely a number of the papules become confluent, with the formation of a large superficial nodule.

The squamous variety is rare. While all of the lesions scale more or less, especially when resolving, yet occasionally there is very profuse formation of scales from the onset. These are closely adherent and are rather fine, of a whitish color.

The discoid lesions are flat, and have very little "body" to them. At times they are disseminated as such over the entire body and face, but they are more apt to be circumscribed in their location. They are also very apt to be scaly.

The moist lesions form the typical condylomata. These lesions are usually situated around the genitalia and anus, and occasionally

beneath the breasts or in the axillæ. They are much more common in women than in men, and in negroes than in whites. A well-developed condylomata is about one centimeter in diameter, is sharply raised from the skin, and has a flat, smooth, moist top, and is of a pale grayish color.

The annular lesions are more apt to occur in negroes than in whites. They are especially common around the angles of the mouth and eyes, but may appear anywhere upon the surface, even upon the mucous membranes. In size they vary from one centimeter to ten or even fifteen centimeters. They may be ringed, or they may be scroll-like, and often there are rings within rings. The edge is raised and covered by whitish scales, and may be broken or continuous. The center may resemble normal skin, it may be pigmented or it may be depigmented. At times the center is simply depressed and covered by thick white crusts. These annular lesions are very common in the colored as both Howard Fox and I have pointed out.

The discoid lesions may at times coalesce so as to form a large plaque, usually a dark red color, and apt to be upon the face.

At times the lesions may become so scaly in a few weeks as to closely resemble psoriasis. These lesions must be sharply differentiated from the late squamous syphilides, which affect the palms and soles.

The papulopustular lesions are simply acuminate or rounded papules in which suppuration has taken place. Not all papules are thus affected; usually only a small percentage of them are. These lesions are very much commoner in negroes than in whites.

The acuminate pustular lesions may have started as papules, or they may have been pustules almost from the onset. They are common in the colored race, and may be very superficial or rather more deeply-seated. They affect all portions of the body, but are nearly always well marked upon the thighs.

In the obtuse lesions there is a fairly large, more or less hemispherical papule that softens in the center, with the formation of pus, and sometimes of a considerable crust.

In the ecthymoid lesions there are depressed ulcers, covered by crusts of varying thicknesses; when the crusts resemble an oyster shell they are spoken of as rupia. Ordinarily, however, the crusts resemble those seen in impetigo contagiosa, or ecthyma but are



rather more adherent. When removed it will be seen that there is an underlying clean cut, rather deeply punched out ulcer.

Macular syphilis resembles two conditions, pityriasis rosea and a drug rash. Pityriasis rosea has a much brighter color than has syphilis, the lesions are oval, and the long axis runs parallel with the direction of the ribs. In typical cases the lesions of pityriasis clear in the center, becoming yellowish, while the edges are a bright rosy color. Even in the atypical cases the varying sizes of the lesions, their bright color, early scaliness and direction should serve to make the diagnosis clear.

Drug rashes are usually bright in color and itch or burn. These facts, coupled with the history of drug taking, should make possible a proper diagnosis.

The papular variety is almost characteristic. Occasionally an eczema will confuse, but the itching of the latter, coupled with its more circumscribed distribution, should serve to settle the question. Lichen planus has different lesions; they are angular, umbilicated and arranged in rows, and are often of a purplish color.

The papulosquamous lesions may resemble psoriasis, but in the latter disease the site of predilection is the extensor surfaces of the limbs, and the course is very chronic. Seborrhoeic eczema likewise has special areas that it prefers to attack—the scalp, midline of the face, axillæ and groins, as well as the midlines of the chest and back. The lesions are dark red and are often covered with greasy scales.

The superficial pustules are to be distinguished from drug rashes, from acne and from smallpox. The drug eruptions are usually not generalized, but chiefly involve the face and body; there is a history of drug taking and other signs of syphilis are wanting. Acne is chronic, its lesions usually having been present for many years; it involves the face and back, and more rarely the chest. The presence of blackheads around which the lesions invariably form should serve to settle the question.

The deeper pustules must be told from ecthyma. All that is necessary is to remove the crust and look at the ulcer beneath; in ecthyma it is superficial and irregular, while in syphilis it is deep and punched out. Ecthymatous lesions are usually confined to the legs and are common in children, not in adults.

At times it may be rather difficult to distinguish smallpox from pustular syphilis, but as a rule there should be very little trouble.

The eruption of smallpox is most profuse upon the face and hands, and the palms are nearly always involved. The pustules are deep-seated, and have a hard, shotty feel. There is usually fever and backache. In syphilis there is an initial lesion, and usually other evidences of syphilis, the palms are usually not involved and while the lesions are moderately infiltrated they are not as hard as in smallpox.

Nodular syphilis is the same thing as the "tubercular syphilis" of the textbooks and earlier writers. Curiously many students and physicians have become imbued with the mistaken idea that tubercular syphilis is a combination of tuberculosis and syphilis, hence it seems better to drop the term "tubercular."

The agminate lesions are the rounded conical papules or nodules of late syphilis. When they first appear they may be discrete, but they usually run together to form a patch or raised nodule. These lesions are most common upon the face and limbs, but frequently develop upon the trunk as well. They vary in size at the onset from 4 mm. to 1 cm. in diameter, but when confluent may be four or five centimeters in size. These lesions may become covered by heavy scales and are then known as squamous. They may resolve spontaneously with or without scar formation; when scars are left they are known as cicatricial lesions.

It hardly seems worth while to separate the circinate and serpiginous lesions. Both consist primarily of agminate lesions, that extend peripherally or by the formation of new lesions so as to form round or serpiginous patches that may attain a diameter of from four to ten or twelve inches. They are most common upon the limbs and body. These patches usually clear up in the center, with or without the formation of scar tissue. Ulceration may or may not take place at the edge. The course is always extremely slow, and the lesions are usually painless.

The squamous lesions occur primarily upon the palms and soles; they are doubtless primarily nodular, but the thickness of the skin makes them appear squamous. These lesions usually come on late in the course of syphilis, but may occur as early as one year after infection. At first there are a number of isolated thickened patches, usually in the lines; then some scaling and cracking occurs, and the patches extend so that they usually become confluent. The edge is well-defined, and there may occasionally be ulceration at the border.

The color is a deep red, and there are some whitish overlying scales. The lesions develop very slowly and are exceedingly rebellious to treatment. They are always difficult to tell from eczema.

The gummous lesions are the true gummata of the skin. Gummata are probably most common upon the upper third of the lower leg, especially upon the anterior and outer aspects, but also arise with great frequency upon the scalp, forehead, arms and body; in fact practically anywhere. There may be only one lesion, or there may be a dozen or more. A gumma commences as a deep-seated node that is inflammatory in appearance, but only slightly painful. In the course of a week or ten days it has usually made its way to the surface, when central necrosis takes place, with the formation of a deep, punched out ulcer, that at first is under a centimeter in diameter, but that may become much larger. The ulcer is usually round, and the walls extend at right angles to the skin, which does not overhang. There is very little induration in the majority of cases, the base is usually fairly clean, and there is but little discharge unless secondary infection occurs. At times these lesions are rather shallow, and are covered by thick crusts that are laminated like oyster shells; they are then called rupial lesions. Occasionally the lesions become distinctly verrucose, but this is rare.

The tuberos gummata develop more superficially than do the typical gummata, and are especially common upon the face. They develop into patches that may be an inch or more in diameter. In the negro the follicular openings are frequently very marked. These lesions may persist for some years, but usually they break down within six months. The diffuse gummous syphilide is comparable to the diffuse changes occurring in the tongue and viscera. An area of five or six inches in diameter may be involved in a gummous development, primary in the corium. At first the skin is a livid red color, with deep infiltration, which may subsequently break down, forming typical ulcers.

A gumma must be diagnosed from an abscess, from erythema nodosum and occasionally from cancer. An abscess is more acute and more painful, and the resulting ulcer is of irregular shape, not being cleanly punched out as in the ulcer of syphilis. Erythema nodosum is usually symmetrical, occurs chiefly upon the legs, and does not break down. The edge of a gumma is usually soft, while that of a carcinoma is stony hard; a gumma develops more rapidly

than a cancer. An injection of arsphenamine will clear up a gumma, but will not influence a cancer.

The nodular lesions must be told from tuberculosis and cancer. Lupus begins in early life and spreads very slowly, very much more slowly than does syphilis; it usually attacks the face. Cancer develops after forty, and has a rolled edge of stony hardness; its spread is very slow.

The differential diagnosis between squamous eczema of the palms and squamous syphilis is often extremely difficult. Eczema is usually symmetrical, syphilis may be unilateral; eczema usually itches, especially after washing, while syphilis only rarely itches. Both have sharp-defined margins, and both look very much alike. It is usually necessary to resort to the laboratory before one can be absolutely certain.

## ENLARGEMENT OF THE LOWER LIP FROM SYPHILIS

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(Received for publication, November 25, 1921.)

BESIDES the typical luetic papule or small, or large gumma, there occasionally arises, in certain regions, a diffuse syphilitic infiltration. The lower lip is especially subject to this and the deformity produced is so striking as to constitute a valuable diagnostic feature. This enlargement is seldom mentioned, but judging by photographs of the oral region as seen in works on syphilis, it would seem to be fairly frequent. The very prominent lower lip is too often present to be merely a coincidence. The accompanying photograph shows the enlargement accompanied by tertiary luetic papules. The subject of it, a man forty-two years of age, in good general health, presented himself for treatment on October 24, 1921.

The trouble had appeared two years previously on the outer surface of the lower lip toward the left side, where there was now a large patch of thickly set, pea-sized luetic papules. This patch not alone involved the skin but also the mucous membrane of this region. As can be seen in the photograph, there were other scattered papules and nodules. For instance, there were two papules to the left of the chin and a patch of them to the right, and there were two symmetrically situated gigantic nodules on the upper lip, one of which stood above each corner of the mouth. The Wassermann reaction was strongly positive. As is usual in tertiary syphilis, no matter how great the local tumefaction may be, there was no demonstrable swelling of the lymphatic nodules.

The thickened, out-rolled lower lip with its rough, desquamating surface was, however, an outstanding feature of the case. For the patient it was the dominant symptom, as besides being uncomfortable, it prevented playing the cornet, on which he depended for part of his living. In fact, he ascribed his trouble to playing this instrument.

The only history of syphilis was a vague statement in regard to

the patient's father, but the patient himself showed no stigmata of hereditary lues.

The very first effect of the treatment was to render the lip more manageable, and the morning following the first infusion of arsphenamine the patient, to his great joy, was able to whistle, a pleasure denied him for many a long month. Of course, this speedy action of arsphenamine is nothing new, but is a never-failing cause of astonishment that it can so quickly influence anything so chronic and substantial as the infiltrative lesions of tertiary syphilis.

This regional hypertrophy due to syphilis may occur either in the foot or leg, in the external genitalia of the female or in the lip and lower part of the face.

Purposely, in this article the term, syphiloma, has been avoided, because in the lip, in the case under discussion, the enlargement resembled more a swelling than a tumor. In the vulva, however, as shown recently by Arthur Stein, the tumorlike appearance and sluggish progress often present justifies the name, syphiloma vulvae.<sup>1</sup> The tumefaction and induration here may be gigantic, and in shape may resemble a horse collar. These masses are not entirely reducible by antisyphilitic remedies but may require surgical removal. In the external genitalia and in the lower extremity these enlargements have a complicated etiology. In the latter region varicose veins, and the consequent ulceration, together with streptococcic infection contribute a notable part, and in the female genitalia venereal traumatism and gonorrheal infections are often present. In the lower lip, however, as in the above example, the enlargement is usually entirely due to the luetic virus, and is a manifestation of treponemal angiotrophism. The virus follows along outside the blood vessels, giving rise to encircling sleeves of round-celled infiltration, and it is the multiplicity of these that constitutes the hypertrophy. The anatomic reason, therefore, for the occurrence of this enlargement of the lower lip is the richness of this region in blood vessels. This, therefore, is only one more example of the fondness these microorganisms show for the blood vessel walls, and is in line with the frequent invasion of the heart muscle, of the aorta and of the blood vessels of the brain. Indeed, the chancre itself in this region shows this tendency to deep swelling, causing the spoutlike projection of the lower lip and the snoutlike projection of the upper one. In the chancre, however, the



Fig. 1.—Showing the enlarged lip, outrolled and roughened. Around the mouth there are a number of late nodular syphilides, both scattered and in groups. One group lies under the left corner of the mouth and another to the right of the chin. There is a large nodular syphilide above each corner of the mouth.





swelling is localized and not diffuse, excepting in the labium maius, where it may give rise to the striking phenomenon of edema indurativum, so excellently illustrated by Buschke.<sup>2</sup>

In the above case the hypertrophy was combined with, but not due to, a late papular and nodular syphilide, for at only one point had the papules invaded the red of the lip. The other papules were below the lip or laterally removed from it. In this it differed from chancral enlargement, which is decidedly part of the chancre itself, although probably due to the same angiotrophism.

As in the vulva so in the lip, the hypertrophy may exist as the sole local symptom, and may spread to the chin and cheeks, and give an elephantiasic appearance to the face; this condition is called tertiary luetic leontiasis, or diffuse hypertrophic syphiloma.

In the leg the hypertrophy may be followed by a smooth atrophy called by Finger, liodermia. This is a very rare occurrence.

This labial enlargement has, however, more than an academic interest. It is useful in diagnosis. Not long ago a man past middle age called at the office with a nodular lesion on the red of the lower lip. As such tumors are almost invariably epitheliomas, this conclusion was momentarily arrived at, till it was noticed that the lip was more enlarged in its entirety than it should be. It was then perceived that the nodular lesion was made up of a group of small nodules in various stages of evolution, and that its situation alone prevented it from being instantly recognized as a grouped tubercular syphilide.

There is another interesting point in regard to this infiltration. Under treatment the nodular syphilides disappear with startling rapidity, but these perivascular infiltrations are by far more persistent, and require a much more prolonged treatment to clear up their last vestiges.

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## ROENTGENOLOGY OF SYPHILIS IN BONE

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(Received for publication, December 12, 1921.)

THE reader is asked to consider two pertinent facts which seem to manifest themselves throughout this discussion upon the roentgen analysis of syphilis in bone.

- (1) Syphilis in bone is usually a constructive osteoplastic process.
- (2) The extent of the recorded roentgen involvement in syphilis of bone is rarely paralleled by the clinical symptoms. In other words, the clinical findings are not as extensive as the x-ray findings. This is not the fault of the clinician but the character of the disease.

To anticipate argument one must grant that osteoporosis luetica of the skull is frequently a destructive process. However, an analysis of the complete roentgen history of such cases provides events in their career in which osteoplastic evidence is obtained. This will receive further attention under the proper heading.

Before engaging in the intimacies of the roentgenology of syphilis in bone, it may be well to provide the reader with an analytic scheme for classifying the shadow values of all bone lesions.

- (1) Bone lesions cast shadows which are *constructive* in osteomyelitis and syphilis.

- (2) Bone lesions cast shadows which are *destructive* in tuberculosis and malignancy.

- (3) Bone tumors which are *constructive* are usually *benign*: bone tumors in which *destructive* changes predominate are malignant. It is realized that this analytic scheme is broad and subject to valid criticism. At the same time it is urged that the more one tries to stick to this scheme, the easier one will arrive at a true analysis of shadow values in bone as projected upon the roentgen plate.

This scheme anticipates that (1) the analyst will look upon the roentgen plate without clinical bias; (2) that he will determine whether he is looking upon a destructive or a constructive process; (3) that he will then analyze his constructive lesion into the osteomyelitic or syphilitic group and the destructive lesion into the

tuberculous or malignant group; and (4) lastly, then attempt to prove by further analysis, *plus the clinical picture*, that the lesion has *not* been correctly grouped.

It is realized that this scheme may appear bizarre because of its simplicity. It does not parallel, in the least, the analytical method of Baetjer. It may, however, serve as an antithetic check for those familiar with Baetjer's scheme. Baetjer's scheme is thoroughly expounded in the recent text book by Baetjer and Waters and is more intimately concerned in the analysis of bone tumors.

To engage ourselves, however, under the title of "The Roentgenology of Syphilis in Bone" the subject may be divided into topics:

- (1) Generalizations.
- (2) Syphilis of the Long Bones.
- (3) Syphilis of the Skull.
- (4) Syphilis of Joints.
- (5). Differential Shadow Values.

(1) *Generalizations*: The bone lesions of syphilis may be rated as constructive processes in all except syphilitic lesions of the plates of the skull. Some may analyze Charcot Joint as a destructive process and this is partly true but the great amount of calcareous debris thrown out at the enlarged joint may serve to keep the rule of the constructive nature of syphilis in bone.

Osteoporotic changes in the tables of the skull are usually typically syphilitic and are simulated by malignancy only. The differentiation is usually simply a matter of history, age and possible metastasis. A primary malignancy of the skull tables is rare. Syphilitic osteoporosis is usually found in the pre-cancer ages.

The constructive character of syphilitic bone shadows is seen in the laminated calcareous veiling of the bones of the hand or foot and nominated syphilitic dactylitis. These are distinctly the opposite shadow values to the tubercular spina ventosa which shows areas of softening and local caries within a slightly expanded bone outline.

The sabre tibia is a typical constructive process. The cortical zone casts a dense bony shadow which is characteristic. Even though there be localized ulcers or gumma present as surface complications there is always a dense background of lime deposits which are rather evenly distributed.

The long bones of infants and children frequently present the parallel veiling of the shaft characteristic of syphilis. It appears as though the osteogenetic zone of the periosteum was evenly elevated as a dense opaque line, leaving a thin narrow zone of transparency enveloping the normal bone cortex.

The key-note, therefore, of luetic bone lesions is osteoplasia. Contrasting conditions, such as tuberculosis and malignancy, produce loss of bone salts or halisteresis. Syphilitic lesions produce sharp and dense shadows while tuberculosis gives poor photographic results on account of the lypomacia. The atropic changes of disuse must not be overlooked.

(2) *Syphilis of the Long Bones*: Syphilis of the long bones is always an osteoplastic constructive process.

The sabre tibia is an excellent and characteristic example in acquired lues. There is no encroachment of the lesion upon the medullary portions but a laying down of dense bony tissue in the cortical and periosteal zones. There may be localized gummata or seemingly encapsulated areas of softening (bone blisters) but the grand characteristic of a constructive process is never lacking.

In congenital syphilis of the long bones, manifested usually within the first year of age but possible up to eight or ten years of age, one notes the characteristic veiling of the shaft by the shadow of the osteogenetic periosteal tissues. This veiling is parallel to the shaft. There is very little deformity of the limb. The swelling of the soft parts is mildly uneven but without the tumefaction or redness seen in osteomyelitis. There is no evidence of destruction of the cortex or medullary portions of the bone as long as the parallel veiled appearance persists. If ulceration or syphilitic necrosis develops beneath the periosteum, there is an immediate answer of the cortex in the laying down of calcium deposits and a closing of the transparent space between the periosteum and the cortex.

The luetic dactylitis is a characteristic congenital lesion and corresponds to the descriptions in the preceding paragraph. Differentiating luetic dactylitis from tubercular spina ventosa sometimes requires minute analysis and is not always accomplished. One expects to find destructive shadows in the shaft with tuberculosis while the shaft remains clean in syphilis. The veiling in syphilis is always a laying down of parallel lines while the elevated shadow of the

periosteum in tubercular spina ventosa is an expansion or ballooning of the periosteal membrane about a destructive lesion in the shaft.

(3) *Syphilis of the Skull*: Syphilitic lesions of the skull occur: (1) in the tables with various degrees of involvement; (2) in the base with the characteristic saddle-nose; and (3) as hydrocephalus with the enlarged contour. The roentgen ray records the deformities of the latter two divisions but, obviously, adds nothing to the case history.

The syphilitic lesions of the tables may vary from osteoporosis to osteoplasia depending upon the mode of reaction of the tissues to the syphilitic invasion or to the period in the career of this reaction. An osteoporotic lesion may develop into an osteoplastic lesion or it may proceed to sequestration and infiltration of the soft parts. The lesion may develop as osteoplastic tophi without osteoporotic changes beneath and these appear upon the roentgen plate as so much putty laid down upon otherwise normal shadows of the bone plates of the skull.

Schüller has observed flat swellings consisting of granulation tissue between the bone and the periosteum of the flat cranial bones beneath these tophi. When these tophi heal there is extensive osteophytic production to fill up and eliminate the preceding osteoporosis. This results in a marked sclerosis and thickening of the tables.

The gummatous lesions of the skull may be localized or extensive and usually in the flat bones of the skull. If there gummata proceed to heal there is a development of osteophytes and sclerosis.

It will be seen, therefore, that the roentgen picture of lues of the skull tables depends upon the stage of the disease in which it is radiographed.

The author has encountered a characteristic skull picture-syndrome which may accompany the increased intracranial pressure of cerebrospinal syphilis. (1) The skull tables are generally thickened; (2) the diploeic channels are prominent and the diploeic lake of the parietal eminence is increased in dimensions; (3) there are serrations like herring-bones along the superior margins of the parietal bones in the lateral roentgen plate; and (4) possibly the faint scalloped outlines of compressioni digitorum upon the inner tables. These shadows may possibly be explained as follows:

- (1) The thickened skull is the result of a slow osteoplastic process.
- (2) The increased diploeic channels are due to introcranial pressure with the demand for more space in the venous channels of the diploe.
- (3) The herring-bone serrations are osteophytic developments.
- (4) The scalloping of the inner table by intracranial pressure is vividly shown in hydrocephalus but in the above condition these scallops are not well defined.

It is well to reiterate that the above picture-syndrome is not pathognomonic but has been observed with sufficient frequency as to be noticeable in cerebrospinal syphilis. It frequently is encountered in late developing epilepsy.

(4) *Syphilis of Joints*: There may be characteristic roentgen shadows to joint syphilis but there is only unanimity of opinion in the roentgen findings of acquired osteoarthropathy or Charcot's joint. This is usually an incident in the career of tabes dorsalis. The leading roentgen shadows indicate atrophic erosion of the joint surfaces by attrition and the irregular deposit of calcium salts in and about the confines of the enlarged joint. Rarely is this condition mistaken because the other clinical symptoms of tabes dorsalis are exhibited. It may be possible that the x-ray examination of a traumatized joint will anticipate the clinical manifestations. The abnormal flexibility of the early Charcot joint and the atrophic changes in the bones forming the joint with increased density to the diaphyseal portions of bones should warn one as to the eventual development of a typical Charcot joint. These changes were encountered by the author in a case which did not develop a classical tabes dorsalis until three years later.

The joint lesions of hereditary syphilis do not cast diagnostic shadows. They are confused with tuberculosis and infectious osteochondritis. Differential points bear discussion. Tuberculosis usually displays a decalcification throughout the component parts of the joint with poorer photographic results at the center of the exposed plate than at the circumference. In tuberculosis there is a single joint involvement. In syphilis this decalcification is not so marked. In fact there is a seeming reaction in the tissues of the diaphysis which provides increased density and therefore the seeming atrophy at the joint is only relative. With syphilitic joints there is frequently a hydrops, and there may be more than one joint involved

but this latter point is not of sufficient value for any dependence. The destructive changes in joint syphilis are rarely commensurate with the severity of the symptoms and there are usually signs of reaction or resistance just beyond the joint confines.

The joint changes of the primary and secondary stages of syphilis are not recorded upon the x-ray plate as they are not persistent and are confined to the soft parts. The shadows are only of negative value as a means of diagnostic exclusion of other destructive pathology. This may be of great importance, however, to the clinician.

(5) *Differential Shadow Values*: It may be well to reiterate or restate the fact that joint lesions of syphilis other than Charcot joint rarely show violent destructive changes but lean toward hypertrophic pathology with perhaps an isolated area of softening in a localized gumma. The zone of proliferative constructive reaction can be determined. This may confuse syphilis with infectious osteochondritis, such as Perthes' disease or Koehler's disease, but not with tuberculosis. Even the close analysis of many published failures of orthopedists to read their roentgen plates correctly seems to indicate that there has not been sufficient attention to the roentgen characteristics of bone tissue reaction to syphilitic or tubercular invasion.

The desirability of making repeated roentgen exposures of bone lesions to determine the effect of diagnostic therapy should not be overlooked. The reaction of bone syphilis to proper therapy is usually rapid. On the contrary the progress of a tubercular disease is not very great in the same interval of time, perhaps a few weeks.

It is suggested that one look upon the two great confusing diseases of syphilis and tuberculosis of bones and joints from another angle. Bones seem to display a resistance to syphilitic invasion by piling up a positive resistance or a zone of defense. While in tuberculosis there is a negative resignation to the progress of the invader.

# STUDIES IN THE STANDARDIZATION OF THE WASSERMANN REACTION. XXIII\*

## A STUDY OF METHODS FOR CONDUCTING QUANTITATIVE COMPLEMENT-FIXATION TESTS AND OF READING SCALES FOR RECORDING REACTIONS

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(Received for Publication, November 30, 1920.)

SINCE the Wassermann reaction has become widely adopted as an index of the severity of infection with *T. pallidum* and as guide to treatment, a measure of the degree of complement fixation or strength of a positive reaction with serum and cerebrospinal fluid is generally demanded. A standardized complement-fixation test must fulfill this requirement and in a more satisfactory manner than is possible by methods in common use at the present time.

### ANALYSIS OF PRESENT METHODS

*One Tube Method.*—Probably the majority of serologists follow the principles of a quantitative method gradually evolved from the work of Wassermann and Citron, that is, Wassermann's one tube test with Citron's method of reading the reactions as strongly positive, weakly positive, doubtful and negative. Citron uses three tubes (the third being the serum control) and the same scheme for recording the reactions, but most serologists use but one dose as in Wassermann's test and Citron's scheme of recording the strength of the reaction.

Contrary to general opinion *this method is only partially quantitative*. For example, a serum may contain four units of syphilis antibody and give a ++++ or strongly positive reaction; a second serum may contain ten units of antibody but cannot give a result stronger than the same ++++ reaction. In other words, a certain amount of antibody is required to give a ++++ reaction in any given test conducted with a fixed amount of serum as 0.1 or 0.2 c.c.; if the

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\*Investigation aided by funds accruing from the preparation of arsphenamine.



serum contains more than this amount of antibody, it is not shown in the reaction. Only when the amount is reduced below this amount may the reactions gradually become weaker as +++, ++, + and negative.

In practice, the serum of a patient yielding a ++++ or strongly positive reaction before treatment is instituted may continue to react in this manner for an indefinite period until the amount of antibody is reduced to the +++ level; this may give the physician reason for suspecting that treatment is having no effect at all upon the strength of the reaction, whereas more accurate quantitative methods employing graded doses of serum or complement may show that the amount of antibody is actually being reduced.

A one tube test (that is a front or antigen tube and a rear tube for the serum control) is satisfactory for determining whether or not a serum or cerebrospinal fluid contains syphilis antibody, but yields only a rough gauge of the amount of antibody. For this reason, I prefer to call it a *qualitative* rather than a *quantitative* test for the reasons given above. This test is perfectly satisfactory for determining whether or not a fluid yields a positive or negative reaction, but as a measure of the degree of positiveness it is unsatisfactory and should give way to more accurate quantitative tests.

*Complement Unit Method.*—Browning and McKenzie<sup>1</sup> titrate complement for the unit of hemolytic activity and conduct the complement fixation test in a series of test tubes carrying a fixed amount of serum and antigen with an increasing number of units of complement; the anticomplementary activity of each serum and the antigen are measured separately according to the number of units of complement fixed or absorbed by each and the sum of these is subtracted from the number of units fixed by mixtures of serum and antigen to give the strength of the reaction.

The method is very satisfactory and with a few modifications not involving the essential principles, has yielded good results in my hands. The main advantages are the strictly quantitative character of the test and the possibility of examining anticomplementary sera; the main disadvantages are the expense involving the use of large amounts of complement serum when many sera are to be tested and difficulties in reading, permitting considerable variation due to the personal equation.

*Serum Dilution Method.*—Many serologists follow Citron's plan of using two doses of serum but as previously stated this method is only partially quantitative; Boas<sup>2</sup> uses a series of dilutions of serum yielding a better quantitative test.

The main advantages of a quantitative method based upon using each serum or cerebrospinal fluid in a series of amounts ranging from the largest which will "pick up" small amounts of antibody to the smallest amount at which the majority of sera containing large amounts of antibody will give a negative reaction, are those of economy, convenience and speed with which the tests may be conducted. The main disadvantage is the possible influence of natural hemolysins in the largest amount of serum; with cerebrospinal fluid this objection does not hold and even with sera, this influence may be neutralized by easily applied technical details.

*Antigen Dilution Method.*—It is also possible to conduct a quantitative test by using each serum in a series of test tubes in a fixed amount with a fixed amount of complement and varying amounts of antigen, ranging from one to ten antigenic units.

I have tried this method and found it inferior to the complement unit and serum dilution methods; there are no particular advantages whereas the slight changes in antigenic activity of an extract from week to week interferes with the accuracy of results with the smaller amounts of antigen. Furthermore, it is more difficult to adjust the dose of complement to the test whereas when one dose of antigen is employed, the complement is readily adjusted by titration in the presence of antigen. Finally, experience has shown that the strength of an antigen is not always proportional to the dose so that reactions with large amounts of antigen may be weaker than with smaller amounts.

*Method Based upon Rapidity of Complement Fixation.*—Complement is rapidly fixed by large amounts of syphilis antibody and antigen and Simon<sup>3</sup> has recently described a somewhat quantitative test based upon the principle of rapidity of complement fixation. The objection to the method, however, is the time required when a large number of sera are to be tested at one time.

#### METHOD PROPOSED FOR A STANDARDIZED TECHNIC

*After extensive comparative tests with all of these methods, the decision has been reached that the serum dilution method is best for*

*a standardized technic from the standpoints of economy, accuracy and ease of manipulation.*

A very large number of tests were required before a decision could be reached regarding the proper amounts of serum and spinal fluid to use. The objects sought for in this work were as follows:

*First, to have the maximum amount of serum or spinal fluid large enough to "pick up" the smallest amounts of antibody and yet avoid nonspecific reactions and particularly the anticomplementary reactions.* In our technic 0.1 c.c. serum and 0.5 c.c. spinal fluid were found satisfactory and equivalent approximately to 0.6 c.c. serum and 3 c.c. spinal fluid in terms of the original Wassermann test. Advantage has been taken therefore, of using relatively large amounts of serum and spinal fluid for increasing the delicacy of the reactions; at the same time extensive experience has proved that these amounts are perfectly safe.

*Secondly, to have the smallest amount of serum and spinal fluid in the series of dilutions small enough to give less than a ++++ reaction with sera and spinal fluids yielding very strongly positive Wassermann reactions;* under these conditions the range of doses will give a true measure of the antibody. In our test these minimum amounts have been found to be approximately 0.001 c.c. serum and 0.035 c.c. spinal fluid.

*Thirdly, to confine the whole range of dilutions of serum and spinal fluid to six tubes including the serum control.* This number of tubes for each quantitative test is reasonable whereas if eight to twelve tubes are used, the objections of excessive labor and use of materials may be raised.

The results of an extensive series of experiments have shown that a good range for sera under these conditions is 0.1, 0.02, 0.004, 0.002 and 0.001 c.c. with 0.1 c.c. for the serum control. As will be noted the second tube contains one-fifth of the maximum amount contained in the first tube; the third tube contains one-fifth of the amount in the second tube while the fourth and fifth tubes contain one-half the amount in the preceding tubes. Experience has shown that with the technic employed the antibody is quickly diluted out of action with amounts of serum less than 0.02 c.c. and for this reason the subsequent amounts are one-half each preceding dose.

With spinal fluids a range of 0.5, 0.25, 0.125, 0.0625 and 0.03125

c.c. with 0.5 c.c. in the control, has been found uniformly satisfactory for a quantitative test.

*Fourthly, to make these quantitative tests as economical as possible in the use of serum and spinal fluid; only 0.3 c.c. serum and 1.5 c.c. spinal fluid are required and a technic has been developed whereby the range of dilutions of each serum and spinal fluid is made with rapidity and accuracy.*

It should be emphasized that *these amounts of serum and spinal fluid have been found satisfactory in our particular technic*; they may not be satisfactory in other methods employing a different kind and amount of antigen, a different primary incubation and different hemolytic system.

While it is true that six tubes for a test demands more labor and time than the usual two tubes, the actual difference in practice is slight and more than compensated by the improvement in results. For the purpose of determining whether or not a serum or spinal fluid does or does not give a positive reaction with a rough gauge of the degree of positiveness, the ordinary two tube or qualitative method is satisfactory; when a more accurate quantitative method is desired and especially as a serological guide for treatment, the serum dilution method can be recommended. In the method to be proposed as a standardized technic<sup>4</sup> both qualitative and the above-mentioned quantitative methods are described, adaptable to antisheep, antiox, antihuman or antichickens hemolytic systems.

#### METHODS FOR INTERPRETING AND RECORDING COMPLEMENT FIXATION REACTIONS

Complement fixation reactions are generally recorded according to the degree of hemolysis or amount of nonhemolyzed corpuscles. This is usually judged by naked eye inspection of the tubes; Lyon and Eiman<sup>5</sup> have described a method of more accurate measurement of nonhemolyzed corpuscles by centrifuging in special tubes and Ivy,<sup>6</sup> a method for measuring the degree of hemolysis by means of a colorimeter.

Two schemes for recording are widely employed; probably the best known is that credited to Citron in which the reactions are recorded somewhat as follows:

- ++++ ( 100 per cent inhibition of hemolysis or strongly positive)
- +++ ( 75 per cent inhibition of hemolysis or moderately positive)
- ++ ( 50 per cent inhibition of hemolysis or weakly positive)
- + ( 25 per cent inhibition of hemolysis or very weakly positive)
- ± ( 10 per cent inhibition of hemolysis or doubtful)
- (complete hemolysis or negative)

These graduations are only practical in "large volume" tests, that is, in the original Wassermann test or such as use a sufficient number of corpuscles to show the different reactions with reasonable accuracy.

The second method is that employed by Craig and Vedder and widely adopted for tests conducted with an antihuman hemolytic system:

- ++ ( 100 per cent inhibition of hemolysis)
- + ( 50 per cent inhibition of hemolysis )
- ± ( some inhibition of hemolysis but less than 50 per cent )
- ( complete hemolysis )

Boas<sup>2</sup> prepares a hemoglobin scale to be used for recording the degree of hemolysis but his method is defective because it does not take into account such modifying factors as the antigen, complement and serum.

Bergeron and Normand<sup>7</sup> have overcome this objection by hemolyzing ten different doses of corpuscles with hemolysin and corpuscles and adding antigen and serum to each tube, giving a series of ten shades and permitting an accurate measurement of the degree of hemolysis.

Terry<sup>8</sup> has described a method of aiding naked eye readings and particularly differentiation among +++, ++ and + reactions by using tubes of uniform size (1 cm.) and reading at night holding the tube close to the eye, 18 to 24 inches from a 110 volt 25 to 40 Watt unfrosted Mazda bulb and looking for the filaments of the bulb. In a negative reaction the filaments are clearly seen; in a + they are also visible whereas in a ++ reaction they are invisible. For differentiation between a ++ and a +++ a specially constructed 3 mm. pipet is used in the same manner. The principle is good, but the technic requires too much time when a large number of quantitative tests are being conducted, the majority giving

positive reactions. The reading scale proposed in this article has been found as satisfactory and much less time consuming.

METHOD PROPOSED FOR RECORDING STANDARDIZED COMPLEMENT  
FIXATION REACTIONS

As previously mentioned the technic to be proposed as a standardized method employs five doses of serum and cerebrospinal fluid; the test is conducted with 0.5 c.c. of a 2 per cent suspension of corpuscles in a total volume of 3 c.c. These amounts easily permit the estimation of 100, 75, 50 and 25 per cent inhibitions of hemolysis corresponding to + + + +, + + +, + + and +.

In our quantitative test employing five amounts of serum and spinal fluid the degree of positiveness or inhibition of hemolysis is recorded for each amount. With each dose of serum or spinal fluid the reaction may be read + + + +, + + +, + +, + or - giving a two-way quantitative test employing five dilutions with a scale of five readings on each, as per the following example with the serum of an untreated syphilitic in the secondary stage.

0.1	c.c. serum = + + + +
0.02	c.c. " = + + + +
0.004	c.c. " = + + +
0.002	c.c. " = +
0.001	c.c. " = -

The above reaction may be recorded as 4431 -.

After six intravenous injections of 0.6 gm. arsphenamine at intervals of one week, the test yielded the following reactions, which may be recorded as 431 - -:

0.1	c.c. serum = + + + +
0.02	c.c. " = + + +
0.004	c.c. " = +
0.002	c.c. " = -
0.001	c.c. " = -

The cerebrospinal fluid of a case of tabes dorsalis showed the following reactions, recorded as 44421:

0.5	c.c. fluid = + + + +
0.25	c.c. " = + + + +
0.125	c.c. " = + + + +
0.0625	c.c. " = + +
0.03125	c.c. " = +
0.5 (control)	c.c. " = -

After a course of treatment embracing mercurial inunctions, potassium iodide and twelve intravenous injections of arsphenamine, the reactions were as follows, recorded as 4431 -:

0.5	c.c. fluid = ++++
0.25	c.c. " = ++++
0.125	c.c. " = +++
0.0625	c.c. " = +
0.03125	c.c. " = -

The strongest possible reactions with serum or cerebrospinal fluid would be recorded as 4 4 4 4 4 and negative reactions as -----; so far we have found but few sera and no spinal fluids out of many hundreds of tests, yielding a 4 4 4 4 4 reaction so that the range of doses appears satisfactory from the standpoint of a quantitative test.

Experience has shown that reactions with this technic may be interpreted as follows:

(a) *Very strongly positive* when positive reactions of *any degree* occur with the first four or all five dilutions as +++++ or ++++-.

(b) *Strongly positive* when the reactions are positive in *any degree* with the first three dilutions, as +++--.

(c) *Moderately positive* when the reactions are positive in *any degree* with the first two dilutions, as ++---.

(d) *Weakly positive* when the reactions are positive in *any degree* with the first or largest amount of serum or spinal only, as +----.

(e) *Negative* when the reactions are negative throughout, as -----.

In this technic the reactions are read about two hours after the secondary incubation; this interval permits the partial but sufficient settling of corpuscles. The primary incubation is eighteen hours at 8° C. which divides the test into two days; if an additional twenty-four hours were allowed for the settling of corpuscles the time would be unnecessarily prolonged.

#### READING SCALES

With practice one may readily learn to read +++++, +++, ++, + and - reactions with the different doses of serum and spinal fluid; but persons working in different laboratories read with slight differences, rendering the use of a color scale distinctly advantageous from the standpoint of uniform readings.

Attempts to produce more or less permanent color scales with

glycerin and gelatin have proved unsatisfactory; simple solutions of corpuscles in distilled water or after hemolysis by complement and hemolysin are likewise unsatisfactory because they do not show the modifications of color due to antigen, complement, etc.

A perfect reading scale should at least include the following:

1. The corpuscles of the day showing varying degrees of hemolysis.

2. The complement, because it is usually slightly tinged with hemoglobin and other pigments.

3. The antigen, which imparts an opalescence.

4. The patient's serum, because it is usually tinged with hemoglobin and other pigments.

The hemolysin is not necessary in an antishoop or antioox system because it is usually so highly diluted (1:500 or higher) as to be colorless; with the antihuman or antichickien hemolytic systems, the hemolysin may be included if used in fluid form, because they are generally employed in dilutions of about 1:50 or less.

With most of the reading scales so far proposed, only solutions of hemoglobin have been employed; experience has shown, however, *that reading the reactions according to the degree of hemolysis (color of supernatant fluid) and degree of inhibition of hemolysis (nonhemolyzed corpuscles) is actually easier and somewhat more accurate from the standpoint of uniformity of readings of the same reactions by different persons.*

Therefore, in the reading scales devised for the standardized complement-fixation test both hemoglobin and corpuscles are included in addition to complement and antigen; the only ingredient omitted is serum because (1) some sera are apt to be just a little different in color from the majority and more especially because (2) each is used in five different amounts. Cerebrospinal fluid being practically colorless is likewise omitted.

The reading scale is composed of five tubes showing + + + +, + + +, + +, + and - reactions with the ingredients (corpuscles, antigen and complement) of each day's work. It is prepared at the close of the primary incubation and placed in the water-bath during the secondary incubation in order to equalize all conditions. The scale shows the proper degree of hemolysis and whole corpuscles and requires but a few minutes for its preparation. It has been found particularly useful for aiding naked eye readings of +, + + and + + + reactions. In order to avoid repetition a detailed description of the



technic is given with that of the method to be proposed as a standardized complement-fixation test.<sup>4</sup>

#### SUMMARY

1. An accurate *quantitative* complement-fixation test for syphilis is essential to show the severity of infection and the effect of specific treatment.

2. Complement-fixation tests conducted with one or two doses of serum or spinal fluid and fixed doses of antigen and complement after the original Wassermann technic, are only partially quantitative in character.

3. Of the three main quantitative methods proposed employing varying amounts of complement, varying amounts of serum or varying amounts of antigen, best results have been observed with a quantitative method employing varying amounts of serum or cerebrospinal fluid.

4. In the proposed quantitative method employing graded amounts of serum and spinal fluid, the maximum amount of each yields a very delicate specific reaction in the presence of but traces of antibody; the smallest amount of each gives less than a ++++ reaction with large amounts of antibody and thereby yields a satisfactory quantitative reaction for practical work.

5. A reading scale is of value for recording the results of complement fixation reactions and should contain the same corpuscles (hemolyzed and nonhemolyzed), complement and antigen employed in each set of complement fixation tests.

6. The principles of a quantitative complement fixation test and reading scale proposed for a standardized technic are described.

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## STUDIES IN THE STANDARDIZATION OF THE WASSERMANN REACTION. XXV\*

### A SUPERIOR ANTIGEN FOR COMPLEMENT-FIXATION TESTS IN SYPHILIS (A CHOLESTEROLIZED AND LECITHINIZED ALCOHOLIC EXTRACT OF HEART MUSCLE)

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(Received for publication, November 30, 1920)

AS STATED in a previous article<sup>1</sup> extracts prepared by mixing alcoholic solutions of acetone insoluble lipoids (lecithins; phosphatids) and cholesterin proved best as antigens for the Wassermann test, being highly antigenic and but slightly anticomplementary and hemolytic. Alcoholic extracts of heart reenforced with cholesterin were usually of equal antigenic value, but more anticomplementary and hemolytic; alcoholic solutions of acetone insoluble lipoids alone were as satisfactory insofar as anticomplementary and hemolytic activities were concerned, but were less antigenic. Plain alcoholic extracts of heart muscle and fetal syphilitic liver were much less antigenic, more hemolytic and equally anticomplementary.

Due to the investigations of Noguchi,<sup>2</sup> Browning, Cruickshank and McKenzie,<sup>3</sup> Erlandsen,<sup>4</sup> Neymann and Gager<sup>5</sup> and others, we now know that the lecithins (diaminomonophosphatids) are highly antigenic and very slightly hemolytic and anticomplementary and Noguchi's method for extracting these from tissues (acetone insoluble lipoids) is highly efficient and somewhat preferable to the more complicated procedure of Browning, Cruickshank and McKenzie. As shown by Erlandsen and Neymann and Gager, ether removes from tissues a large portion of the hemolytic substances, principally soaps, neutral fats and fatty acids; also bile salts in extracts of liver tissue. Alcohol also removes some of these in addition to substances possessing marked anticomplementary activities, as proteins and protein cleavage products cholesterol and other lipoidal

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\*Investigation aided by funds accruing from the preparation of arsphenamine.

bodies and various salts. No doubt some of the latter are also antigenic but at least the best of them namely, cholesterol, can be prepared in a high state of purity and added to any extract for the advantage of its influence upon antigenic activity.

#### PRINCIPLES OF THE METHOD FOR PREPARING THE NEW ANTIGEN

The following method utilizes these observations and the results of previous studies on antigens<sup>1</sup> and yields extracts of remarkable antigenic sensitiveness and slight anticomplementary and hemolytic activity; the principles of the method are as follows:

1. Dried human or beef heart muscle is employed; there is no choice between the two tissues if both are *perfectly fresh*. Human heart muscle, however, is frequently fatty or may have undergone more or less postmortem change; if so, fresh lean beef heart muscle is to be preferred. Dried tissue is employed for the following reasons: (a) It permits of the use of very finely divided tissue; (b) tissues are easily kept for long periods of time; (c) three or more heart powders may be kept, permitting of the use of mixtures of tissues and polytropic extracts which are probably better than preparing an extract of a single heart muscle.

2. The dried tissue is first extracted with ether, which removes a large portion of the hemolytic substances; the phosphatids (lecithins) which are also partly removed by the ether are recovered by precipitation with acetone and returned to the extract.

3. The tissue is now dried and extracted with alcohol which removes some antigenic and hemolytic substances and considerable anticomplementary substances. This alcohol is evaporated, extracted with ether and precipitated with acetone, which removes the highly antigenic fraction of lecithins (phosphatids), which are later returned to the extract.

4. The tissue is now extracted for a second time with absolute ethyl alcohol which removes some antigenic principles and slight or almost negligible amounts of anticomplementary and hemolytic substances. The acetone insoluble lipoids (lecithins, phosphatids) recovered from the preliminary ether and alcohol extractions are dissolved in ether and returned to this alcoholic extract with 0.2 per cent cholesterol; the resulting extract possesses high antigenic activity, slight anticomplementary and frequently no hemolytic activity.

## TECHNIC FOR PREPARING THE ANTIGEN

*Drying of Tissue.*—Fresh beef or human hearts are washed free of blood, dissected free of fat and large blood vessels and the muscle passed through a meat grinder three or four times. The minced tissue is then rapidly dried in a vacuum apparatus or equally well by spreading in *thin layers* on clean glass plates and drying by *rapid fanning, preferably* in a dust proof box, for eighteen to twenty-four hours, turning the layers after the first ten to twelve hours. The cakes of dried material are now broken up, placed in an incubator overnight and ground into a fine powder, which is kept in tightly stoppered bottles of colored glass at room temperature. *Three or more hearts may be prepared at one time and a mixture of the powders used in preparing extracts. Rapid drying is essential to prevent decomposition which results in greatly increasing the hemolytic activity of the extracts.*

*Extractions.*—(a) Twenty-five grams of powdered muscle are extracted with about 100 c.c. of ether in a Soxhlet for eighteen hours; if this apparatus is not available, the powder is extracted with 200 c.c. of ether in a tightly stoppered bottle at room temperature for five days, being shaken occasionally each day. The ether is carefully removed and saved for the time being in a tightly stoppered bottle.

(b) The powder is now dried by fanning for a few minutes or by spreading on a glass plate for several hours, placed in a bottle and extracted with 200 c.c. of 95 per cent alcohol in an incubator for four days.

(c) The alcohol is carefully decanted, poured into a flat shallow dish and fanned dry. The residue is extracted with 30 to 50 c.c. of ether for the ether soluble portion; this ethereal extract is covered and allowed to stand for an hour or two for the heavy insoluble particles to settle out.

The ethereal solution is now mixed with the ether of primary extraction and the mixture concentrated by fanning until reduced to about one quarter volume or about 25 to 30 c.c. Six volumes or about 150 c.c. of pure acetone are now added to the concentrated ether which throws down a whitish precipitate; the mixture is covered and placed aside for several hours or overnight for the complete separation of the acetone insoluble portions. On the following day the supernatant acetone is decanted and the sticky residue of ace-

tone insoluble lipoids removed and kept in acetone in a tightly stoppered wide-mouthed bottle for future use.

(d) The muscle powder is now extracted for a second time with 100 c.c. of absolute acetone free ethyl alcohol in an incubator for six days guarding against evaporation and shaking the mixture once or twice a day and if possible for at least one day in a mechanical shaker; the extract is now filtered through fat-free paper.

*Finishing the Antigen.*—Two-tenths gram pure cholesterol (Kahlbaum's preferred) and all of the acetone insoluble lipoids previously prepared, are dissolved in 10 c.c. of pure ether and the cloudy brownish mixture slowly added to the filtered alcoholic extract and well shaken. The extract is now placed in the incubator for a few hours or overnight, being shaken occasionally and then at room temperature for a day or two; the light brownish precipitate is now removed by filtration through fat-free paper or by decanting the extract. The finished antigen is kept in a tightly stoppered brown glass bottle in the laboratory, or in a refrigerator. Any precipitate forming after this time is left undisturbed.

#### PROPERTIES OF EXTRACT

Titration of the intermediate and final products for hemolytic, anticomplementary and antigenic activities with a technic described elsewhere,<sup>6</sup> has usually shown the following:

1. Primary ether extract:
 

Hemolytic	0.6 c.c. of 1:5
Anticomplementary	0.5 c.c. of 1:5
Antigenic	0.1 c.c. of 1:10
2. Primary alcohol extract:
 

Hemolytic	1.0 c.c. of 1:5
Anticomplementary	0.6 c.c. of 1:5
Antigenic	0.1 c.c. of 1:25
3. Secondary alcohol extract:
 

Hemolytic	not in 1 c.c. of 1:5
Anticomplementary	0.9 c.c. of 1:5
Antigenic	0.1 c.c. of 1:25
4. Finished extract:
 

Hemolytic	not in 1 c.c. of 1:5
Anticomplementary	0.7 c.c. of 1:5
Antigenic	0.1 c.c. of 1:150

The above results indicate the following: 1. The primary ether extraction removes considerable of the hemolytic and some of the anticomplementary and antigenic principles.

2. The primary alcoholic extraction also removes some of the hemolytic, anticomplementary and antigenic substances.

3. The secondary alcoholic extract is much less hemolytic and anticomplementary than the primary alcoholic extract while being equal in antigenic activity (sometimes greater).

4. The secondary alcoholic extract reenforced with the acetone-insoluble lipoids (lecithins; phosphatids) and 0.2 per cent cholesterol is not any more hemolytic but is slightly more anticomplementary (due to cholesterol) than the alcoholic extract alone; its antigenic activity is greatly increased, the antigenic unit being one hundred to three hundred times less than the anticomplementary and hemolytic units.

*The finished extract easily permits the use of at least ten antigenic units as the dose to be employed in the conduct of complement fixation tests with a standardized technic, this amount being at least ten to thirty times less than the anticomplementary and hemolytic units and rendering the test for syphilis highly sensitive without the danger of nonspecific reactions.*

#### COMPARATIVE VALUE OF EXTRACT

A study of the properties of the new antigens has been made in a series of comparative tests employing the usual antigens of plain and cholesterolized alcoholic extracts of heart muscle, alcoholic extracts of fetal syphilitic liver and acetone insoluble lipoids of heart muscle (3 per cent solutions in methyl alcohol as prepared by Noguchi).

The results of one experiment are shown in Charts I and II as examples of the series; Chart I gives the comparative hemolytic and anticomplementary values and Chart II, the comparative antigenic values.

In conducting the hemolytic titrations varying amounts of each extract diluted with saline solution, were mixed with 0.2 c.c. of 5 per cent sheep cells and saline added to make the total volumes 2 c.c.; the results were read after one hour at 38° C. In Chart I are shown the smallest amounts of each antigen producing slight hemolysis.

In the anticomplementary and antigenic titrations an antishoop system was employed with a primary incubation of eighteen hours at 8° C.; in Chart I are given the smallest amounts of each antigen

Chart 1.- Comparative Hemolytic and Anticomplementary Activities of Various Antigens.

Amounts 1:5	Alc. Ext. Syph. Liver	Alc. Ext. Beef Heart	Cholest. Alc. Ext. Beef Heart	Acetone Insoluble Lipoids	New Antigen
0.1					
0.2					
0.3					
0.4					
0.5	H				
0.6					
0.7					
0.8	A				
0.9					
1.0					
*	H	A	H	A	H

\* H = hemolytic unit; A = anticomplementary unit.

Chart 2.- Comparative Antigenic Values of Various Antigens.

Amount 0.1 c.c.	Alc. Ext. Syph. Liver	Alc. Ext. Beef Heart	Cholest. Alc. Ext. Beef Heart	Acetone Insoluble Lipoids	New Antigen
1:400					
1:300					
1:250					
1:200					
1:150					
1:100					
1:50					
1:25					
1:10					
* Primary incub.	W R	W R	W R	W R	W R

\* W = water bath 1 hour; R = refrigerator at 8 C. for 18 hours.

producing slight inhibition of hemolysis (anticomplementary unit). Chart II shows the smallest amounts producing absolute inhibition of hemolysis with 0.05 c.c. of heated syphilitic serum (antigenic unit) with primary incubations of one hour in a water-bath and eighteen hours in a refrigerator at 8° C.

As shown in these charts the new antigen has been found superior to those commonly employed, being very highly antigenic and remarkably free of the objectionable hemolytic and anticomplementary properties.

In these respects the new antigen approaches one of the requirements of an ideal extract somewhat more closely than the extracts in common use; furthermore, being prepared of a mixture of dried muscles from several hearts and containing but 0.2 per cent cholesterolin, these extracts are highly polytropic and have never yielded negative complement-fixation reactions, when tested with a series of antigens yielding positive reactions with the sera of syphilitic persons. For this reason the new antigen may be safely relied upon alone and the necessity for using multiple antigens in the conduct of the Wassermann test for the sake of accuracy, is thereby removed.

The new antigen keeps remarkably well either in a refrigerator or at room temperature.

All of a series of antigens prepared as described have proved worthy, fit for use and possessing about the same antigenic hemolytic and anticomplementary values; so far not a single extract has failed.

The new antigen is not as cheaply prepared as simpler extracts owing to the alcohol, ether and acetone employed, but when considered in view of the large amount of finished extract (100 c.c.) and the very small amount necessary for a complement-fixation test, the expense is relatively small.

The technic of preparation is simple although more laborious than the preparation of simple alcoholic extracts; it is scarcely more laborious however, than the preparation of acetone insoluble lipoids as described by Noguchi and Bronfenbrenner.

#### SUMMARY

1. A new antigen is described prepared of mixtures of dried powdered muscles of several beef or human hearts; the hemolytic and anticomplementary activities are largely removed by primary ether and alcohol extractions, the antigenic principles of these being recovered by precipitation with acetone and returned to a secondary alcoholic extract with 0.2 per cent cholesterol.

2. The resulting cholesterolized and lecithinized alcoholic extract



of heart is polytropic, keeps well, is very highly antigenic and but slightly hemolytic and anticomplementary; different extracts are uniform in these properties.

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# STUDIES IN THE STANDARDIZATION OF THE WASSERMANN REACTION. XXX\*

## A NEW COMPLEMENT-FIXATION TEST FOR SYPHILIS BASED UPON THE RESULTS OF STUDIES IN THE STANDARDIZATION OF TECHNIC

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THE complement-fixation technic described in this communication represents the results of nearly six years of continuous investigation upon the subject of standardization of technic.

The method of study pursued as expressed in the first paper<sup>1</sup> "was to become acquainted with all existing methods by thoroughly reviewing the available literature and by means of personal communications and interviews with a large group of serologists and *submitting the whole to careful unbiased experiment and choosing that proving best on the basis of actual trial.*"

"Realizing the complex nature of the Wassermann reaction and the variable properties of its several biological reagents, our almost complete ignorance of its mechanism and the absence of a specific and wholly satisfactory antigen, the task of even attempting standardization was considered a serious and laborious problem; *knowing that the majority of serologists had an individual way of conducting certain steps in the technic and particularly that many had learned from experience to rely so firmly upon their own method as to be very loath to accept any other,* the hope of building up a widely acceptable technic would appear almost hopeless unless an unexpected discovery bestowed upon the standard technic an indisputable quality of excellence."

From this quotation taken from my first paper, it is plain that I originally shared the skepticism of serologists regarding the possibility of really standardizing the Wassermann reaction; with such diversity of opinion among serologists on almost every step in

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\*From the Dermatological Research Laboratories of Philadelphia.  
Investigation aided by funds accruing from the preparation of arsphenamine.

technic this appears almost hopeless, although highly desirable. However, the technic herein described is believed to rest upon well established principles, has been successively practiced for over a year and I hope at least merits unprejudiced trial, "thereby aiding in arriving at a conclusion regarding its status as an acceptable standard technic for the Wassermann reaction."

## Part 1

### REQUIREMENTS OF A STANDARD WASSERMANN REACTION AND HOW THESE HAVE BEEN FULFILLED BY THE NEW TECHNIC

In my opinion the essential requirements of a standard technic as expressed in the first paper may be summarized as follows: 1. As high degree of sensitiveness as is permissible with specificity; (2) practical specificity; (3) technical accuracy and uniformity in results; (4) yield a quantitative reaction; (5) simplicity in technic; and (6) economy.

An attempt has been made to fulfill all of these requirements in the new technic by the following procedures:

#### MEETING THE REQUIREMENT OF SENSITIVENESS

1. *By the Use of a Highly Sensitive Antigen.*—This is of paramount importance and the new extract previously described<sup>25</sup> has been found almost free of hemolytic activity, very low in anticomplementary activity and very highly antigenic, permitting:

2. *The Use of Large Amounts of Antigen.*—At least ten antigenic units of the new antigen may be used with entire safety, this amount being twenty times or more less than the anticomplementary and hemolytic units and yielding very sensitive but true reactions. A large amount of time has been devoted to a study of different kinds of antigen, their manufacture<sup>24</sup> and preservation<sup>26</sup>; also to the proper amount to use from the standpoint of securing the greatest degree of sensitiveness consistent with true reactions.<sup>27 28</sup> With the new extract ten antigenic units has to be the optimum amount to use.

3. *By Using Relatively Large Amounts of Serum and Spinal Fluid in the Test.*—This phase has required a great deal of investigation<sup>23</sup> because there are limits to be placed upon the amounts to employ because: (1) The introduction of serum constituents other than antibody may interfere with complement fixation; (2) excessive

amounts may result in nonspecific reactions due to the anticomplementary activities of serum and spinal fluid, and (3) reduce sensitiveness by the introduction of natural hemolysins and hemagglutinins. To these may be added: (4) the question of economy.

Most serologists use 0.1 to 0.2 c.c. serum and 0.4 to 1.0 c.c. spinal fluid; the original Wassermann test requires 0.2 c.c. serum and 0.4 c.c. spinal fluid. Calculated in relation to the amount of complement employed, the largest amount of serum employed in the new test, namely, 0.1 c.c., corresponds to about 0.3 to 0.4 c.c. in terms of the original Wassermann test and the largest amount of spinal fluid, namely, 0.5 c.c., corresponds to 1.5 to 2.0 c.c. Extensive trials have shown that *for routine work* the use of these amounts results in the greatest possible degree of sensitiveness to be expected on the basis alone of amounts of serum and spinal fluid employed. Economy is discussed later.

4. *By Heating Sera for Only Fifteen Minutes at 55° C. Instead of for Thirty Minutes.*—As stated in a previous paper<sup>13</sup> we found it necessary in routine work to heat sera for the purpose of: (1) removing anticomplementary substances; (2) removing the possibility of nonspecific proteotropic reactions; and (3) removing native complement and depending upon a mixture of guinea pig complements. These objects are secured by heating for fifteen minutes at 55° C. unless a serum is older than four days or improperly preserved, when thirty minutes may be required for the removal of antilysins. *Heating for fifteen minutes results in much less destruction of syphilis antibody* and has been found uniformly satisfactory when tests are conducted *every three or four days, the specimens of blood kept in a refrigerator and the serum left on the clot until used. Spinal fluids are used unheated.*

5. *By Using a Mixture of Guinea Pig Complement Prepared in a Manner Tending to Increase Sensitiveness to Fixation.*—As is well known, guinea pig complement varies in fixability by syphilis antibody and tissue extracts<sup>4</sup>; we have not found it necessary to titrate individual sera for fixability, a mixture meeting the requirements. Human complement also varies in fixability and explains why a syphilitic serum may give a falsely negative reaction in tests employing the patient's own complement; I am convinced that this may occur<sup>6</sup> and it constitutes an important reason for conducting the tests with a *mixture* of the sera of several healthy guinea pigs.

6. *By Mixing Serum and Antigen for a Brief Period before the Addition of Complement* in setting up the test; this appears to slightly increase the sensitiveness of reactions.<sup>18</sup>

7. *By Using a Primary Incubation of Fifteen to Eighteen Hours in a Refrigerator at 6 to 8° C.*—This is of great importance from the standpoint of increasing the delicacy of reactions.<sup>14, 15, 16, 17</sup> It must be emphasized, however, that refrigerator incubation increases non-specific complement fixation and that the hemolytic system must be adjusted accordingly; a hemolytic system adjusted for conducting the primary incubation in a water-bath or thermostat for one hour is not likely to prove satisfactory for the refrigerator method.

Refrigerator incubation of two hours or less with one hour water-bath is better than one hour in water-bath alone, but inferior to 15 to 18 hours in a refrigerator. The adoption of the latter necessarily requires two days for the conduct of tests; this is to be regretted, but the fact remains that it results in better work and is therefore recommended.

8. *By Close Adjustment of the Hemolytic System* in order to avoid excessive amounts of complement and hemolysin.<sup>11, 12</sup> This is accomplished by titrating both hemolysin and complement before the main tests. Guinea pig complement occasionally contains natural hemolysin<sup>4</sup> and this is adjusted for in the new technic by daily titration of hemolysin, the extra work and time required being negligible factors. Complement is titrated in the presence of the antigen, permitting a close adjustment of the dose to employ.

Extensive experiments have shown that *under these conditions and with a primary incubation of 15 to 18 hours at 6-8° C., it is necessary to use two full units of complement and two units of hemolysin in order to obtain sharp, clear, and decisive reactions without danger of nonspecific results.*<sup>11</sup>

9. *By Using an Antisheep or Antiox Hemolytic System.*—I have reached this decision reluctantly and only after a very large number of comparative tests to be reported in a separate paper.<sup>30</sup> There is so much *theoretical* evidence in favor of the antihuman hemolytic system that *only extensive comparative tests have shown most conclusively that with the new technic an antisheep system yields the best and most sensitive reactions.* An antiox system ranks second.

In the new test the question of the influence of natural antisheep hemolysin in the sera and complement is rendered practically neg-

ligible. Furthermore the antisheep system permits the use of such powerful hemolysins easily prepared by the immunization of rabbits,<sup>10</sup> that the amount of complement and hemolytic sera required are greatly reduced. This is an important factor for it appears that the use of relatively large amounts of guinea pig complement and rabbit hemolytic serum demanded by an antihuman system as compared with an antisheep, introduce enough other serum constituents to reduce the degree of complement fixation by syphilis antibody and antigen. Whether or not this is the true explanation, the fact remains that actual comparative tests under rigid conditions have shown the superiority of the antisheep and the antiox hemolytic systems.

10. *By Reading the Reactions within Three Hours after the Conclusion of the Secondary Incubation.*—This permits the partial and sufficient settling of nonhemolyzed corpuscles for the purpose of accurate readings without allowing an excessive amount of hemolysin sometimes represented by natural antisheep hemolysin in a human serum<sup>7, 8</sup> to continue hemolysis as is apt to occur when the tests are placed in a refrigerator overnight before the readings are made.<sup>8</sup>

#### MEETING THE REQUIREMENT OF PRACTICAL SPECIFICITY

The phrase "practical specificity" is used purposely because the Wassermann reaction cannot be rendered biologically or absolutely specific for syphilis alone; positive reactions undoubtedly occur in frambesia or yaws.

However, the new test must avoid nonspecific reactions due to avoidable errors in technic:

1. *By Close Adjustment of the Hemolytic System to a Primary Incubation of 15 to 18 Hours at 6 to 8° C.* in order to supply sufficient complement and hemolysin for nonspecific fixation and yet to detect the slightest degrees of specific fixation by syphilis antibody and antigen.

2. *By Careful Titration of Antigen under Conditions Rendering the Dose Employed Suitable for a Primary Incubation of 15 to 18 Hours at 6 to 8° C.*—The technic is described in this paper.

3. *By Including Controls* in every test and especially serum, antigen and hemolytic controls to detect anticomplementary activities of serum and antigen or defects in the hemolytic system; also corpuscle controls to check the tonicity of the saline solution and fragility of cells. Tests with sera from healthy normal and from

syphilitic individuals should be included as positive and negative controls.

#### MEETING THE REQUIREMENT OF TECHNICAL ACCURACY AND UNIFORMITY IN RESULTS

This has been fulfilled in the new technic by the following procedures:

1. By adopting the principle that *pipetting relatively large amounts of fluid (0.2 to 1.0 c.c.) tends to greater accuracy than measuring smaller amounts (less than 0.2 c.c.)* This appears justified in view of the known inaccuracy of ordinary pipettes and other measures, as well as a wide difference in the skill and care of individual workers. In the new technic the smallest amount of patient's serum or spinal fluid to be measured is never less than 0.2 c.c.; this permits of the use of 1 c.c. pipettes divided into 0.1 c.c.

2. *By using a total volume of 3 c.c. with sufficient corpuscles and test tubes of suitable size to yield clear, sharp and easily read reactions.*

3. *By using a reading scale<sup>23</sup> furnishing hemoglobin in solution and nonhemolyzed corpuscles for reading the finer differences in the degree of hemolysis or no hemolysis.*

In regard to *uniformity in results* it must be emphasized that the anticomplementary activity of serum or spinal fluid is very important in relation to reactions. For this reason tests conducted with portions of the same specimen of blood in different cities cannot be expected to yield absolutely similar results, or even in the same city, if serologists vary in their methods of preserving blood until the tests are conducted.

Two or more serologists working in the same or different laboratories testing portions of a sample of blood or spinal fluid from one person *should agree at least upon the question of positive or negative reactions*; in my experience most variations occur with serums yielding weakly positive reactions. Slight discrepancies in the reports on the *degree* of complement fixation must be expected, inasmuch as the personal equation plays an important part in reading the degree of hemolysis, as it does in matching colors in other lines of work, for example, in hemoglobin estimations and color reactions in general. *Slight discrepancies, however, do no harm so long as the primary question of whether a serum does or does not yield*

*a positive or negative result is untouched* and particularly with serums yielding the borderline weakly positive or doubtfully by negative reactions.

The new test has been found to fulfil this primary requisite and furthermore has yielded remarkably similar reactions in the hands of different serologists working with portions of the same serum or spinal fluids in two different laboratories in Philadelphia.

#### MEETING THE REQUIREMENTS OF A QUANTITATIVE REACTION

This is an important requirement in relation to the Wassermann test as a serological guide to the treatment of syphilis. The ordinary test employing a single dose of serum or spinal fluid is only roughly quantitative and is better designated as qualitative as previously discussed.<sup>23</sup>

A complement-fixation test may be made quantitative by any of three procedures as follows:

- a. Using varying amounts of serum or spinal fluid with constant amounts of complement and antigen.
- b. Using varying amounts of complement with constant amounts of serum or spinal fluid and antigen.
- c. Using varying amounts of antigen with constant amounts of serum or spinal fluid and complement.

The first two are much more satisfactory than the third: the first has been adopted because most economical and equally satisfactory as the others.

In the new technic patients serum is used in the following amounts: 0.1, 0.02, 0.004, 0.002 and 0.001 c.c. with 0.1 c.c. in the serum control. Spinal fluid is used in amounts of 0.5, 0.25, 0.0125, 0.00625 and 0.003125 c.c. with 0.5 c.c. in the control. Extensive trials with varying amounts of serum in the different stages of syphilis and with spinal fluids from cases of neurosyphilis, have shown that these ranges are satisfactory. Our object was to adopt as the largest doses of serum or spinal fluid amounts yielding the most sensitive reactions and for the smallest doses, amounts yielding less than total inhibition of hemolysis in the great majority of cases of syphilis.

Between these extremes are three graded doses making five in all, the control being the sixth tube of the series. Of course a finer quantitative test can be secured by introducing eight tubes carry-



ing 0.1, 0.05, 0.025, 0.0125, 0.00625, 0.003125 and 0.0015 c.c. serum with 0.1 c.c. in the control, but six tubes have proved satisfactory and materially reduces both time and materials required. The reading scale permits reading the results with each of the five different amounts of serum or spinal fluid according to the + + + +, + + +, + +, +, and - method. This technic is quantitative therefore in two directions, namely, by using five graded amounts of fluid to be tested with five possible readings on each.

#### MEETING THE REQUIREMENT OF ECONOMY

This refers to both time and materials. From the standpoint of time required the new test cannot qualify as being economical; from the standpoint of materials it easily qualifies.

The new technic is not a short cut method; I am convinced that the principles involved in complement fixation are too intricate, the reagents too subject to variation and our knowledge of the mechanism of the reaction too meager, to permit the evolution of a short cut and simple test fulfilling the requirements of a standard test. Doubtless the time and labor involved for conducting the new test will prevent its adoption by many serologists, but I have endeavored to adhere to the principle that accuracy should never be sacrificed for speed and labor saving. The new technic provides for a quantitative and a qualitative test; I use the former routinely because it requires but little more time.

Insofar as materials are concerned, the quantitative test requires but 0.3 c.c. serum and 1.5 c.c. of spinal fluid; the qualitative test requires but 0.2 c.c. serum and 1.0 c.c. of spinal fluid.

In the new quantitative test 1 c.c. of guinea pig serum is usually sufficient for examining 6 to 7 sera or spinal fluids; in the qualitative test this amount suffices for at least 15 sera or spinal fluids including all controls. In the original Wassermann test which is a qualitative test only, 1 c.c. of complement is sufficient for testing 8 sera or spinal fluids including the usual controls. Complement is the most expensive reagent and the new test easily meets the requirements of economy in this and all other materials. The amounts of blood corpuscles and hemolysin required are so small as not to be worthy of discussion.

## MEETING THE REQUIREMENT OF SIMPLICITY

As stated in my first paper "simplicity is but a relative term inasmuch as the simplest technic is a complicated problem for the inexperienced and insufficiently trained worker, whereas a more complicated technic is perfectly simple to the experienced serologist."

The new technic introduces only well-known principles and I hope will be accepted as relatively simple; certainly the test can be carried out by a careful and conscientious worker in any laboratory supplied with accurate glassware, a water-bath and a refrigerator.

The simple examination of urine for albumin is a procedure capable of yielding different results in the hands of different workers; the Wassermann test requires a worker who has a working understanding of the principles, who refuses to compromise with something almost as good or almost satisfactory and who conducts his or her work with a reasonable degree of accuracy and skill, refusing to sacrifice these for mere speed.

## Part 2

## TECHNIC OF A NEW COMPLEMENT-FIXATION TEST FOR SYPHILIS

As previously stated every step in the technic of complement fixation in syphilis has been investigated, the results of our studies and conclusions based upon them being reported in separate papers listed in the bibliography. For the purpose of brevity therefore, the technic alone will be described here without giving the reasons therefor, these being given in the other publications to which the reader is referred.

## EQUIPMENT

*Glassware.*— Good *pipettes* are essential; certified pipettes are best, of course, but it is advisable to have a separate 1 c.c. pipette for each serum and the item of expense is apt to be prohibitive. As previously stated the new technic calls for pipetting amounts from 0.2 to 1.0 c.c. in order to reduce error due to inaccurate pipettes.

One c.c. pipettes graduated to the tips are preferred so long as the tips are not chipped; otherwise pipettes graduated to within 2 cm. of the tips are to be preferred as previously described.<sup>2</sup> These pipettes should be divided into 0.05 or 0.01 c.c.

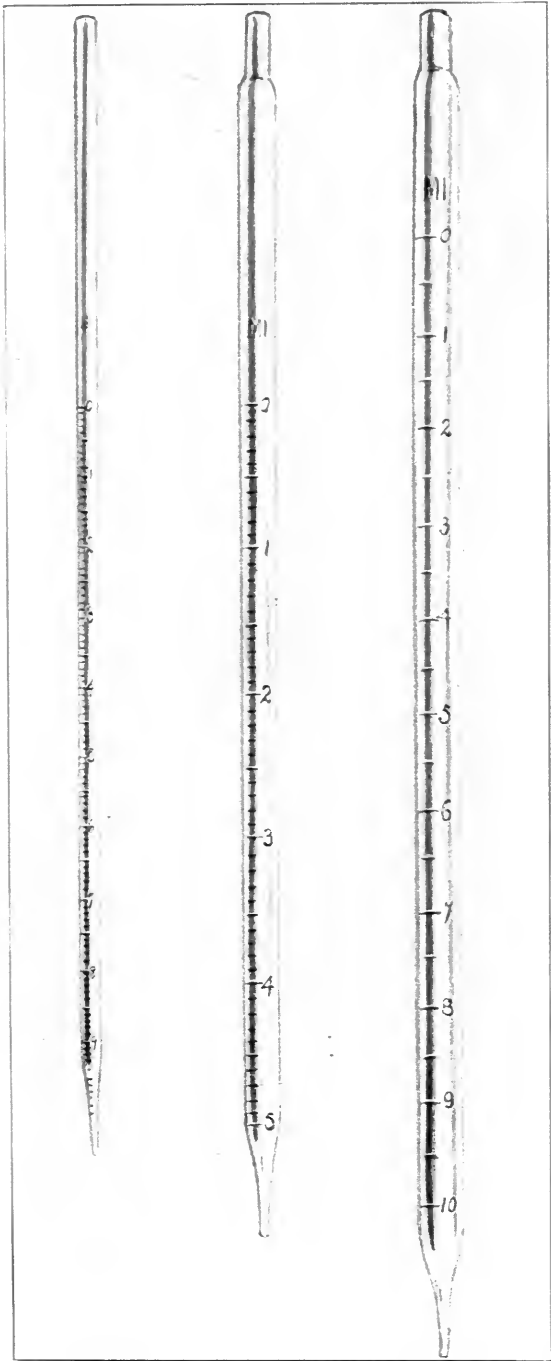


Fig. 1.—Three pipets used by the author for complement-fixation tests; reduced exactly one-half in size.



Five and 10 c.c. pipettes divided into 0.5 c.c. are also required.

Fig. 1 shows these three pipettes\* reduced exactly one half in size; they should be long and slender rather than short and thick.

The *test tubes* should have rounded bottoms, no lips and measure 85 millimeters in length with an internal diameter of 12 to 14 millimeters. It is important that the diameter be within these limits on account of the color scale.

For mixing large volumes, as in the preparation of corpuscle suspension or dilutions of complement serum, *volumetric flasks* rather

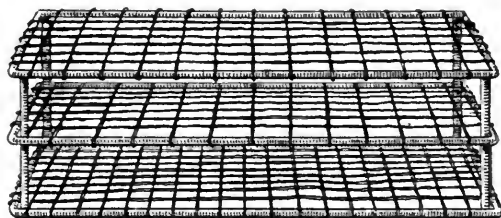


Fig. 2.—A wire rack used by the author for complement-fixation tests, carries 72 tubes.

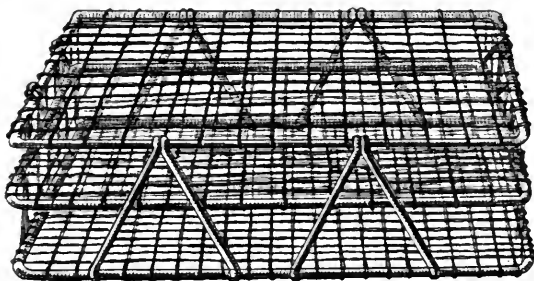


Fig. 3.—A larger wire rack used by the author for complement-fixation tests; carries 144 tubes.

than the ordinary graduated cylinders should be used because of greater accuracy. *The glass-stoppered graduated cylinders* (50 to 100 c.c. capacity) are more convenient, however, for measuring intermediate amounts, and may be used if carefully selected on the basis of accuracy in graduations. For measuring any amount of fluid under 50 c.c. it is better to use an accurate 10 c.c. pipette and reserve the graduated cylinders or flasks for measuring larger volumes.

*It is imperative that all glassware including new glassware should be chemically clean, that is, free of all traces of acids or alkalis and*

\*Made by the Arthur H. Thomas Company of Philadelphia.

preferably sterile; test tubes do not require cotton plugs but may be sterilized in baskets open ends down. A full description of technic for cleaning test tubes and pipettes is given elsewhere.<sup>2</sup>

*Test Tube Racks.*—Each test requires six test tubes. Galvanized wire racks\* (Fig. 2) carrying 12 rows of 6 tubes each have been found very serviceable; also racks carrying 24 rows of 6 tubes each (Fig. 3).

*Water-Bath.*—A simple and inexpensive water-bath for heating sera and conducting the secondary incubation is shown in Fig. 4. A much simpler pan made by any tinsmith is shown in Fig. 5. When carrying water to the depth of 8 cm. the temperature of either pan may be maintained at 55° C. or 37° C. with very little care and attention.

*Refrigerator.*—Any refrigerator maintaining a temperature of between 6 and 8° C. suffices for the primary incubation; electric refrigerators with automatic controls are particularly serviceable.

*Saline Solution.*—Sodium chloride, 0.85 per cent, in water prepared as previously described.<sup>2</sup>

This solution may be prepared as follows:

1. Keep C.P. sodium chloride in a tightly stoppered bottle; if sufficient moisture has collected to render the salt somewhat lumpy, dry a portion in the hot-air oven for ten or fifteen minutes before weighing.

2. Weigh out 8.5 grams and dissolve in 1000 c.c. of freshly distilled water in a chemically clean and dry flask furnished with a gauze-covered cotton stopper; filter through a good paper.

3. Sterilize by heating in an Arnold for an hour; smaller bulks require less heating. (Do not sterilize in an autoclave in order to avoid possible concentration of salt by loss of water in steam.)

4. Before using in the Wassermann reaction it is well to test the tonicity by adding a drop of washed blood cells to 5 c.c. of the solution in a test tube; if there are no immediate signs of lysis or none after gentle mixing and standing aside for half to an hour, the solutions may be accepted.

#### CORPUSCLES (INDICATOR ANTIGEN)

*Two per cent suspension of freshly collected and washed sheep corpuscles; dose 0.5 c.c.*

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\*Made by the Edward P. Dolbey Company of Philadelphia.

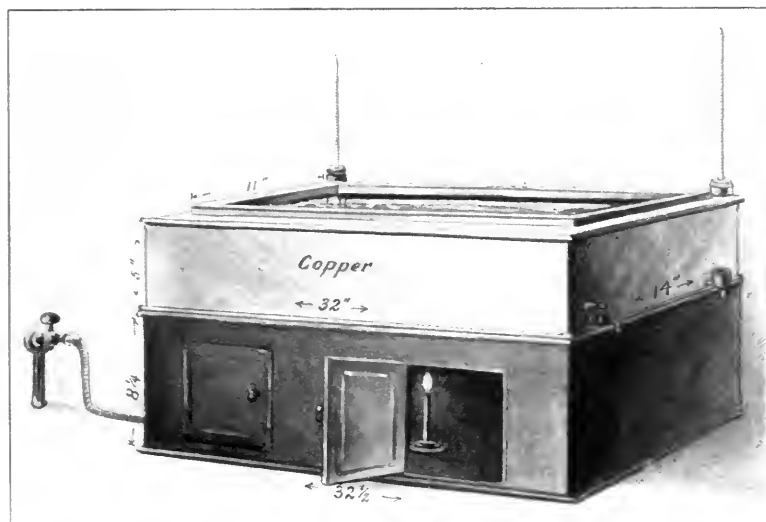


Fig. 4.—A large water-bath used by the author for the secondary incubation in complement-fixation tests; size indicated.

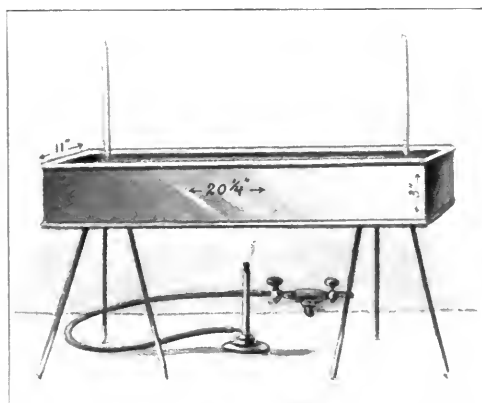


Fig. 5.—A very simple and efficient water-bath used by the author for the inactivation of sera and for secondary incubation; size indicated.





Abattoir blood may be used but *occasionally a worker will encounter corpuscles more resistant to hemolysis than average cells*; for this reason it is better to keep a sheep for furnishing blood but this is by no means necessary. Blood preserved with formalin may be employed under certain conditions<sup>3</sup> but freshly collected blood is better.

Corpuscle suspensions should be fairly uniform and the following method has been found satisfactory; it is not necessary to count the erythrocytes or estimate the hemoglobin as some workers advise, inasmuch as the color scale is prepared of each suspension:

1. In washing defibrinated blood, one volume of blood is placed in a centrifuge tube, two volumes of saline solution added and gently mixed; citrated blood collected in the proportion of one part blood to four parts citrate solution is used without further dilution. Each tube must be accurately counterbalanced in the centrifuge and whirled until all corpuscles have been thrown down, the time required depending upon the speed of the centrifuge (first washing).

2. The supernatant fluid is carefully removed down to the corpuscle mass with a capillary pipette (attached to suction pump or rubber teat) and at least three to five volumes of saline solution added; by capping the tube and inverting, all the corpuscles are thoroughly but gently stirred and mixed in the saline solution and the tubes again centrifuged (second washing).

3. The supernatant fluid is again removed, replaced with saline solution, the corpuscles thoroughly mixed and again centrifuged in accurately graduated tubes\* for *twice as long* as found necessary to throw down the corpuscles in the second washing. This longer period of centrifuging is advisable to firmly and evenly pack the washed cells and *the speed and duration of centrifuging should be uniform in each laboratory as based upon experience with the particular centrifuge in use.*

4. If the supernatant fluid is discolored with hemoglobin, the cells should be washed again until the supernatant fluid is practically colorless.

5. With the last washing the centrifuge is stopped slowly so as not to disturb the corpuscle mass, and the *volume of corpuscles read*

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\*I have devised two sizes of special centrifuge tubes previously described and illustrated (3); these are made by the Edward P. Dolbey Company of Philadelphia and have proved satisfactory.

*in the centrifuge tube before removing the supernatant fluid; the latter is now removed and a suspension of proper strength prepared. A 2 per cent suspension, for example, is prepared by washing the cells from the centrifuge tube into a proper flask with forty-nine times as much saline solution as corpuscle mass.*

6. Sufficient corpuscle suspension should be prepared for the work at hand for the day to obviate the necessity of preparing a second suspension and thereby introducing a possible source of error.

7. As the corpuscles in suspension tend to settle rapidly, the suspension should be *gently and thoroughly shaken* by hand before being used and *during the time of use*, if several minutes are required for pipetting the suspension; otherwise the doses will be uneven and inaccurate.

8. So far as practicable the suspension should be kept in a refrigerator when not being used. A suspension prepared for hemolysin and complement titrations may be kept in a refrigerator until the next day for the main complement-fixation tests.

#### HEMOLYSIN

*Antisheep hemolysin diluted with saline and titrated daily with 0.3 c.c. of 1:30 guinea pig complement and 0.5 c.c. of 2 per cent sheep corpuscles.*

Antisheep hemolysin is easily prepared by the immunization of rabbits, five intravenous injections of 5 c.c. of 10 per cent suspensions of washed sheep blood every five days being a satisfactory method.<sup>10</sup> The animal should be bled seven to nine days after the last injection and the serum preserved by adding an equal part of best grade neutral glycerine, provided a preliminary titration shows that the serum is sufficiently hemolytic, that is, in dose of 0.5 of 1:4000 or higher produces complete hemolysis of 0.5 c.c. of 2 per cent corpuscles with 0.3 c.c. of 1:30 complement in one hour in a water-bath at 38° C.

Most serologists employing an antisheep hemolytic system have reported that the hemolysin requires only an occasional titration; in this technic I have not found this to be the case, owing to variation in the hemolytic activity of complement, variation in the resistance of sheep corpuscles to hemolysis and variation in guinea pig sera. For these reasons I have found it *necessary to titrate the hemolysin each time complement-fixation tests are conducted using*

*the same complement and corpuscles to be employed in the main tests.*<sup>12</sup>

#### COMPLEMENT

*1:30 dilution of the mixed sera of several healthy guinea pigs.*

The complement serum for fixation tests must be: (1) Highly sensitive to fixation by antibody and antigen; (2) possess a high degree of hemolytic activity for the erythrocytes of the indicator antigen and (3) be free or largely so of agglutinins and hemolysins for the cells of the indicator antigen. Studies of the complements of different animals have shown that guinea pig serum is best and the following method can be recommended for collection and preparation; *a mixture of the sera of three or more pigs should be used.*

1. Select large well-nourished animals which have not been fed within twelve to twenty-four hours of the time for bleeding; avoid pregnant animals.

2. Collect blood in a *chemically clean* and preferably sterile centrifuge tube by means of a clean funnel about 4 inches in diameter, or in a Petri dish. We prefer the former because if separation of serum is unsatisfactory the clot may be gently broken up with a glass rod and the serum secured by centrifuging the material. Chemical cleanliness is essential because traces of acids or alkalies are destructive of complement.

3. If guinea pigs are to be bled to death, stunning the animals with a blow at the base of the skull is preferable to ether and chloroform anesthesia because cardiac activity is not interfered with and the maximum amount of blood is obtained. Guinea pigs may also be bled from the ears without anesthesia; or from the heart or an external jugular vein under light ether anesthesia.

4. In bleeding a guinea pig to death it is not necessary to shave the neck; a few hairs in the blood do not alter the properties of the serum. The great vessels on one or both sides should be *quickly* severed and preferably with a pair of stout sharp scissors with one pointed blade to facilitate piercing of the skin and underlying tissues. It is easy to avoid cutting the trachea and esophagus, but it does not appear to make any difference whether the trachea is cut; the esophagus should not be cut because in squeezing the abdomen to pump out blood in the great vessels stomach contents may escape, although even this accident is rare in our experience.

5. In bleeding from the heart a chemically clean and sterilized 5 to 10 c.c. all glass or glass-metal syringe fitted with a short needle of about gauge 20 may be used; in bleeding from an external jugular vein the hairs are plucked just above the region of the clavicle and a small incision made through the skin and vein with collection of blood by means of a funnel into centrifuge tubes. As soon as the animal is released, bleeding ceases and the wound heals promptly and without infection.

6. *Do not use the blood immediately after bleeding*; if the animals are bled on the day the serum is to be used, place the clots in the incubator at 37° C. for an hour followed by breaking up each with a glass rod and centrifuging, or let the clots stand at room temperature for two or three hours for separation of serum which if not complete may be finished by centrifuging. Animals may be bled late in the afternoon of the day before and the clots placed in the incubator for one hour or left at room temperature for two hours and then placed in a refrigerator until the following day. If the sera have separated but poorly, gently break up the clots and centrifuge. *It is preferable to leave the serum on the clot in the refrigerator until ready for use; unused serum should be returned to the refrigerator until required.* Traces of hemoglobin in the serum do not interfere, but the serum should be free of corpuscles.

7. If the work at hand on any day does not require all the serum of three or more pigs it is better to bleed small amounts of blood from the hearts of several large pigs than to use the serum of one animal. If this is not possible, I am convinced that the use of the preserved sera of three or more pigs is better under certain conditions than the use of the fresh serum of a single animal. The following method for preservation can be highly recommended:

*Preservation of Complement.*—To each cubic centimeter of serum collected as described above add 0.3 gm. chemically pure sodium chloride and dissolve; keep in ampules or a dark glass bottle *at or near the freezing point*. When used dilute 1 c.c. with 29 c.c. distilled water which gives a 1:30 dilution in 1 per cent saline. Sera so preserved are good for at least three weeks; possibly for longer periods. *Preserved complements first deteriorate by loss of sensitivity to fixation by syphilis antibody and antigen.*<sup>5</sup>

8. When using fresh complement serum dilute 0.2 c.c. with 5.8 c.c. of saline solution (1:30); this is sufficient for the hemolysin and com-

plement titrations (these require a total of 5.7 c.c.). The balance of serum should be placed in the refrigerator and diluted later (described under complement titration) for the main tests.

#### TITRATION OF HEMOLYSIN AND COMPLEMENT

*Titration of Hemolysin.*—1. Arrange a series of 10 test tubes and place 0.5 c.c. of varying dilutions of hemolysin in each tube, respectively.

2. Ordinarily a range of dilutions from 1:5000 to 1:18000 is sufficient but depending upon the hemolytic activity of the complement and resistance of the corpuscles higher or lower dilutions may be required. A 1:100 dilution preserved with 0.2 per cent phenol against bacterial contamination may be prepared as follows and kept in a refrigerator for several weeks, from which the higher dilutions are prepared as needed:

Equal parts hemolytic serum and glycerin:	2.0 c.c.
Physiological saline:	94.0 c.c.
5 per cent phenol in saline or water	4.0 c.c.

3. The dilutions are prepared as follows in a separate set of large test tubes:

0.2 c.c. of 1:100	+ 1.8 c.c. saline	= 1:1000
0.2 c.c. of 1:100	+ 3.8 c.c. saline	= 1:2000
0.2 c.c. of 1:100	+ 5.8 c.c. saline	= 1:3000
0.2 c.c. of 1:100	+ 7.8 c.c. saline	= 1:4000
0.2 c.c. of 1:100	+ 9.8 c.c. saline	= 1:5000
0.5 c.c. of 1:3000	+ 0.5 c.c. saline	= 1:6000
0.5 c.c. of 1:4000	+ 0.5 c.c. saline	= 1:8000
0.5 c.c. of 1:5000	+ 0.5 c.c. saline	= 1:10000
0.5 c.c. of 1:6000	+ 0.5 c.c. saline	= 1:12000
0.5 c.c. of 1:8000	+ 0.5 c.c. saline	= 1:16000

Mix contents of each tube very thoroughly.

4. Use 0.5 c.c. of each dilution in regulation test tubes and to each add 0.3 c.c. of 1:30 dilution of the same complement and 0.5 c.c. of a 2 per cent suspension of the same corpuscles as used in the complement-fixation tests; add 1.7 c.c. saline to each tube to make the total volume in each 3 c.c.

5. Mix the contents of each tube and place in the water-bath at 38° C. for one hour; *the unit is the highest dilution of hemolysin showing just complete hemolysis. Two units are employed in the titration of complement and antigen and in the complement-fixation tests.*

Table I shows the ensemble and results of a titration.

TABLE I  
TITRATION OF HEMOLYSIN

TUBE	HEMOLYSIN	COMPLEMENT 1:30	CORPUSCLES (2 %)	SALINE	AFTER WATER-BATH INCUBATION FOR ONE HOUR
1	0.5 c.c. 1:5,000	0.3 c.c.	0.5 c.c.	1.7 c.c.	Complete hemolysis
2	0.5 c.c. 1:6,000	"	"	"	Complete hemolysis
3	0.5 c.c. 1:7,000	"	"	"	Complete hemolysis
4	0.5 c.c. 1:8,000	"	"	"	Complete hemolysis
5	0.5 c.c. 1:9,000	"	"	"	Complete hemolysis
6	0.5 c.c. 1:10,000	"	"	"	Complete hemolysis; unit
7	0.5 c.c. 1:12,000	"	"	"	Marked hemolysis
8	0.5 c.c. 1:14,000	"	"	"	Marked hemolysis
9	0.5 c.c. 1:16,000	"	"	"	Slight hemolysis
10	0.5 c.c. 1:18,000	"	"	"	No hemolysis

In the above titration the unit was 0.5 c.c. of 1:6,000; two units were contained in 0.5 c.c. of 1:3,000.

6. Sufficient hemolysin is now prepared for the complement titration and complement-fixation tests so that two units are contained in 0.5 c.c.

*Titration of Complement.*—1. Arrange 10 test tubes and place 0.1, 0.15, 0.2, 0.25, 0.3, 0.35, 0.4, 0.45 and 0.5 c.c. of 1:30 complement in each, respectively; the tenth tube serves as a corpuscle control for this and the hemolysin titration.

2. Into each of the first nine tubes place 10 units of antigen so diluted that this amount is contained in 0.5 c.c.

3. Place sufficient saline solution in each tube to make the total volume about 2 c.c.

4. Mix contents of each tube and place in a water-bath at 38° C. for one hour.

5. Add 0.5 c.c. hemolysin (2 units) and 0.5 c.c. corpuscle suspension (2 per cent) to each tube; mix and reincubate one hour.

6. Ordinarily the smallest amount of 1:30 complement giving complete hemolysis is taken as the unit but *experience has shown that with the method of primary incubation employed in the complement-fixation tests, namely, 15 to 18 hours at 6 to 8° C. this is insufficient; in this test the unit is taken as the amount of complement in the next higher tube.* For example, if hemolysis is just complete with 0.25 c.c. the unit is taken as 0.3 c.c. and double this amount used for the

antigen titrations and complement-fixation tests. For convenience I have designated this amount as *two full units of complement*.\*

Table II shows the ensemble, the results of a titration and the method of reading.

TABLE II  
TITRATION OF COMPLEMENT

TUBE	COMPLEMENT 1:30	ANTIGEN (10 units)	SALINE	HEMOLY- SIN (2 units)	CORPUS- CLES (2 %)	AFTER WATER-BATH IN- CUBATION FOR ONE HOUR
1	0.1 c.c.	0.5 c.c.	1.4 c.c.	0.5 c.c.	0.5 c.c.	No hemolysis
2	0.15 c.c.	"	1.4 c.c.	"	"	Slight hemolysis
3	0.2 c.c.	"	1.3 c.c.	"	"	Marked hemolysis
4	0.25 c.c.	"	1.3 c.c.	"	"	Complete hemolysis; the exact unit
5	0.3 c.c.	"	1.2 c.c.	"	"	Complete hemolysis; the full unit
6	0.35 c.c.	"	1.2 c.c.	"	"	Complete hemolysis
7	0.4 c.c.	"	1.1 c.c.	"	"	Complete hemolysis
8	0.45 c.c.	"	1.1 c.c.	"	"	Complete hemolysis
9	0.5 c.c.	"	1.0 c.c.	"	"	Complete hemolysis
10	—	—	2.0 c.c.	"	"	No hemolysis

*In practice the hemolysin titration may be placed in the water-bath at the same time as the complement titration; at the end of the first incubation of the complement titration the unit of hemolysin is available and two units added to all tubes of the complement titration, etc.*

7. Each two full units of complement are diluted with sufficient saline solution to make 1 c.c. called the dose of complement; for example if 0.3 c.c. of 1:30 complement is the full unit the dose is 0.6 c.c.

A convenient scheme for diluting the dose of complement to 1 c.c. is as follows: divide 30 by the dose = the dilution to employ in dose of 1 c.c.

For example:

Exact unit = 0.25 c.c. of 1:30 dilution.  
Full unit = 0.3 c.c. of 1:30 dilution.  
Two full units = 0.6 c.c. of 1:30 dilution.

$$\frac{30}{0.6} = 1:50$$

\*Experience has shown that in this test the reactions are unsatisfactory if less than 0.4 c.c. of 1:30 complement is employed; occasionally hyperactive sera yield a unit with 0.1 c.c. of 1:30 but when this occurs it is necessary to use 0.4 c.c. for the dose of complement.

If 75 doses of complement were to be provided (sufficient for testing 12 sera or spinal fluids) this would require 75 c.c. of 1:50, prepared by diluting 1.5 c.c. guinea pig serum with 73.5 c.c. of saline solution. This example illustrates the method.

#### TITRATION OF ANTIGEN

The antigen employed in the complement-fixation test for syphilis introduces the most important single factor of variation; the adoption of a certain kind of antigen fulfilling certain requirements is the most important factor in relation to standardization of technic.

In my opinion an antigen should be an alcoholic extract of a fresh tissue and preferably heart muscle reenforced with 0.2 per cent cholesterin;<sup>24</sup> this amount of cholesterin "stabilizes" the extract and greatly increases antigenic activity with very slight or no increase of anticomplementary activity and without increasing the chances for nonspecific positive reactions with heated normal human sera. A superior antigen in my experience is that previously described<sup>25</sup> in which a mixture of dried powder of several heart muscles is used. This powder is first extracted with ether, then with alcohol and again with alcohol; the second alcohol constitutes the base of the antigen which is reenforced with 0.2 per cent cholesterin and all the acetone insoluble lipoids recovered from the ether and primary alcoholic extracts.

*Whatever antigen is employed it should be used in a dose of 10 antigenic units and this amount should be at least 20 times less than the anticomplementary and hemolytic units. A plan for establishing a uniform unit of antigen for use in a standardized test will be described.<sup>29</sup>*

Antigen should be carefully preserved<sup>26</sup> and titrated at least once a month or more frequently if it shows evidences of losing in antigenic activity or acquiring increased anticomplementary activity. *Antigen should be diluted by placing the required amount of physiologic saline solution in a test tube or Erlenmeyer flask and adding the required amount of extract drop by drop or in amounts of 0.1 c.c. and shaking by rotating after each addition.<sup>27</sup>*

*Hemolytic and Anticomplementary Titrations.*—In a series of 10 test tubes prepare the following dilutions of antigen:



1.0 c.c. antigen to 3.0 c.c. saline = 1:4  
 0.5 c.c. antigen to 2.0 c.c. saline = 1:5  
 0.5 c.c. antigen to 2.5 c.c. saline = 1:6  
 1.0 c.c. antigen 1:4 to 1.0 c.c. saline = 1:8  
 1.0 c.c. antigen 1:5 to 1.0 c.c. saline = 1:10  
 1.0 c.c. antigen 1:6 to 1.0 c.c. saline = 1:12  
 1.0 c.c. antigen 1:8 to 1.0 c.c. saline = 1:16  
 1.0 c.c. antigen 1:10 to 1.0 c.c. saline = 1:20  
 1.0 c.c. antigen 1:12 to 1.0 c.c. saline = 1:24  
 1.0 c.c. antigen 1:16 to 1.0 c.c. saline = 1:32

*Hemolytic Titration.*—1. In a series of ten regulation test tubes place 0.5 c.c. of the above dilutions of antigen, respectively.

2. To each tube add 0.5 c.c. of a 1:10 dilution of normal human serum previously heated for fifteen minutes at 55° C. and 1.5 c.c. of saline solution.

3. Mix the contents of each tube and place in a refrigerator at 6-8° C. for 15 to 18 hours.

4. Add 0.5 c.c. of 2 per cent corpuscles suspension to each tube; mix and place in a water-bath at 38° C. for one hour.

5. Allow tubes to stand several hours in a refrigerator and read the results; *the smallest amount of antigen just beginning to produce hemolysis is the hemolytic unit.*

Table III shows the ensemble, the results of a titration and the method of reading.

TABLE III  
HEMOLYTIC TITRATION OF ANTIGEN

TUBE	ANTIGEN 0.5 c.c.	HEATED HUMAN SERUM* 1:10	SALINE	Refrigerator 6-8° C. for 15-18 hours	CORPUS- CLES (2 %)	WATER-BATH 1 HOUR
1	1:4	0.5 c.c.	1.5 c.c.		0.5 c.c.	Marked hemolysis
2	1:5	"	"		"	<i>Slight hemolysis; unit</i>
3	1:6	"	"		"	No hemolysis
4	1:8	"	"		"	No hemolysis
5	1:10	"	"		"	No hemolysis
6	1:12	"	"		"	No hemolysis
7	1:16	"	"		"	No hemolysis
8	1:20	"	"		"	No hemolysis
9	1:24	"	"		"	No hemolysis
10	1:32	"	"		"	No hemolysis

\*May be omitted in which case 2 c.c. saline are added to each tube instead of 1.5 c.c.

*Anticomplementary Titration.*—1. In the first ten tubes of a second series of twelve tubes place 0.5 c.c. of the above dilutions of antigen, respectively.

2. To each of the first eleven tubes add 0.5 c.c. of a 1:10 dilution of *normal* human serum previously heated at 55° C. for fifteen minutes.

3. Add 1 c.c. of diluted complement (carrying two full units) to each of the twelve tubes.

4. To the eleventh tube add 0.5 c.c. and to the twelfth tube 1 c.c. saline solution.

5. Mix all tubes and place in a refrigerator at 6 to 8° C. for 15 to 18 hours.

6. Place tubes in a water-bath at 38° C. for five to ten minutes (not longer) and then add 0.5 c.c. hemolysin (two units) and 0.5 c.c. of the 2 per cent suspension of corpuscles to each tube; mix and place in a water-bath at 38° C. for one hour. Place the tubes in a refrigerator for a few hours and read the results.

7. The *anticomplementary unit* is the smallest amount of antigen producing some inhibition of hemolysis. The eleventh tube is the serum control; the twelfth tube is the hemolytic system control and both should show complete hemolysis.

Table IV shows the ensemble, the results of a titration and method of reading:

TABLE IV  
ANTICOMPLEMENTARY TITRATION OF ANTIGEN

TUBE	ANTIGEN	HEATED HUMAN SERUM* 1:10	COMPLE- MENT (2 full units)	Refrigerator 6-8° C. for 15-18 hours followed by water-bath five to ten minutes	HEMOLY- SIN (2 units)	CORPUS- CLES (2 %)	WATER-BATH 1 HOUR
1	1:4	0.5 c.c.	1.0 c.c.		0.5 c.c.	0.5 c.c.	Slight inhibition of hemolysis
2	1:5	"	"		"	"	Slight inhibition of hemolysis (unit)
3	1:6	"	"		"	"	Complete hemolysis
4	1:8	"	"		"	"	Complete hemolysis
5	1:10	"	"		"	"	Complete hemolysis
6	1:12	"	"		"	"	Complete hemolysis
7	1:16	"	"		"	"	Complete hemolysis
8	1:20	"	"		"	"	Complete hemolysis
9	1:24	"	"		"	"	Complete hemolysis
10	1:32	"	"		"	"	Complete hemolysis
11	0.5 saline	"	"		"	"	Complete hemolysis
12	1.0 saline	-	"		"	"	Complete hemolysis

\*May be omitted and 0.5 c.c. saline added instead.

*Antigenic Titrations.*—1. In a series of ten test tubes prepare the following dilutions of antigen starting with the remainder of the 1:10 dilution prepared above for the hemolytic and anticomplementary titrations:

0.1 c.c. antigen 1:10	to 2.9 c.c. saline = 1:300
0.1 c.c. antigen 1:10	to 3.9 c.c. saline = 1:400
0.1 c.c. antigen 1:10	to 4.9 c.c. saline = 1:500
1.0 c.c. antigen 1:300	to 1.0 c.c. saline = 1:600
1.0 c.c. antigen 1:400	to 1.0 c.c. saline = 1:800
1.0 c.c. antigen 1:500	to 1.0 c.c. saline = 1:1000
1.0 c.c. antigen 1:600	to 1.0 c.c. saline = 1:1200
1.0 c.c. antigen 1:800	to 1.0 c.c. saline = 1:1600
1.0 c.c. antigen 1:1000	to 1.0 c.c. saline = 1:2000
1.0 c.c. antigen 1:1200	to 1.0 c.c. saline = 1:2400

2. Arrange a series of twelve regulation test tubes and place 0.5 c.c. of the above dilutions of antigen into the first ten tubes, respectively.

3. In each of the first eleven tubes place 0.5 c.c. of a 1:10 dilution of a *mixture of equal parts of four or more freshly collected syphilitic and Wassermann positive sera previously heated at 55° C. for at least fifteen minutes.*<sup>27</sup>

4. In each tube place 1 c.c. of diluted complement (carrying two full units).

5. To the eleventh tube add 0.5 c.c. and to the twelfth tube 1 c.c., of saline solution.

6. Mix contents of all tubes and place in a refrigerator at 6-8° C. for 15 to 18 hours.

7. Place tubes in a water-bath at 38° C. for five to ten minutes (not longer) and then add 0.5 c.c. hemolysin (two units) and 0.5 c.c. of the 2 per cent corpuscle suspension to all tubes; mix and place in a water-bath at 38° C. for one hour. Place tubes in refrigerator for a few hours and read the results.

8. The *antigenic unit* is the highest dilution of antigen giving complete inhibition of hemolysis. The eleventh tube is the serum control and the twelfth tube the hemolytic system control; both should show complete hemolysis.

Table V shows the ensemble, the results of a titration and method of reading:

TABLE V  
ANTIGENIC TITRATION OF ANTIGEN

TUBE	ANTIGEN 0.5 c.c.	HEATED SYPHI- LITIC SERA 1:10	COMPLE- MENT (2 full units)		HEMOLY- SIN (2 units)	CORPUS- CLES (2 %)	WATER-BATH 1 HOUR
1	1:300	0.5 c.c.	0.5 c.c.	Refrigerator at 6-8° C. for 15-18 hours followed by water-bath five to ten minutes.	0.5 c.c.	0.5 c.c.	Complete inhibition of hemolysis
2	1:400	"	"		"	"	Complete inhibition of hemolysis
3	1:500	"	"		"	"	Complete inhibition of hemolysis
4	1:600	"	"		"	"	Complete inhibition of hemolysis
5	1:800	"	"		"	"	Complete inhibition of hemolysis
6	1:1000	"	"		"	"	Complete inhibition of hemolysis; unit
7	1:1200	"	"		"	"	Marked inhibition of hemolysis
8	1:1600	"	"		"	"	Marked inhibition of hemolysis
9	1:2000	"	"		"	"	Marked inhibition of hemolysis
10	1:2400	"	"		"	"	Slight inhibition of hemolysis
11	0.5 saline	"	"		"	"	Complete hemolysis
12	1.0 saline	-	"		"	"	Complete hemolysis

9. Ten antigenic units are used in conducting the complement-fixation tests. For example, if the unit is 0.5 c.c. of 1:1000 dilution as shown in Table V, the dose of ten units would be contained in 0.5 c.c. of 1:100 dilution.

#### THE QUANTITATIVE COMPLEMENT-FIXATION TEST

1. Sera should be properly prepared<sup>19</sup> and heated in a water-bath at 55° C. for fifteen minutes;<sup>13</sup> spinal fluids are used unheated. The tests should be set up in the following order: serum first, followed by antigen, and lastly by complement.

2. For each *serum* arrange six regulation test tubes and place saline solution in the following amounts respectively: 1.2, 0.8, 0.8, 0.5, 0.5 and 0.5 c.c.

(a) Into the first tube place 0.3 c.c. serum and mix by drawing up in pipette and expelling at least three times. Transfer 0.5 c.c. to tube No. 6 and 0.2 c.c. to tube No. 2; discard 0.3 c.c. (b) Mix No. 2 and transfer 0.2 c.c. to tube No. 3 and discard 0.3 c.c. (c) Mix No. 3

and transfer 0.5 c.c. to tube No. 4. (d) Mix No. 4 and transfer 0.5 c.c. to tube No. 5. (e) Mix No. 5 and discard 0.5 c.c.

Each tube now contains 0.5 c.c. carrying 0.1, 0.02, 0.004, 0.002, 0.001 and 0.1 c.c. (serum control).<sup>19</sup>

3. For each *spinal fluid* arrange six regulation tubes and place 0.5 c.c. saline in Nos. 2, 3, 4, 5 and 6.

Into the first, second and sixth tubes place 0.5 c.c. spinal fluid; mix No. 2 and transfer 0.5 c.c. to No. 3; mix No. 3 and transfer 0.5 c.c. to tube No. 5. (e) Mix No. 5 and discard 0.5 c.c.

Each tube now contains 0.5 c.c. carrying 0.5, 0.25, 0.125, 0.0625, 0.03125, and 0.5 c.c. (control).<sup>19</sup>

4. Into the first five tubes of each set add 0.5 c.c. antigen dilution (carrying ten antigenic units).

5. After an interval of five to thirty minutes<sup>18</sup> add 1.0 c.c. of complement to each tube (carrying two full units).

6. Include the following controls: (a) *antigen control* tube carrying 0.5 c.c. of the diluted antigen, 1 c.c. of the diluted complement and 0.5 c.c. of saline solution; (b) *hemolytic system control* carrying 1 c.c. of the diluted complement and 1 c.c. of saline solution; (c) *corpuscle control* carrying 2 c.c. of saline solution; (d) *positive* and *negative* serum controls should be included using syphilitic and normal sera, respectively, set up in the various amounts as described above.

7. Start the preparation of a reading scale as follows:

a. Heat 6 c.c. of the diluted complement in a water-bath at 55° C. for 15 minutes.

b. Prepare a solution of hemoglobin by dissolving 2 c.c. of the 2 per cent corpuscle suspension in 4 c.c. of plain water.

c. Arrange a series of five regulation test tubes numbered 1 to 5 and place in each: 0.5 c.c. of the diluted antigen and 1 c.c. of the heated diluted complement.

d. Add hemoglobin solution to the first four tubes as follows: 1.5, 1.13, 0.75 and 0.38 c.c.

e. Add 0.24 c.c. physiologic saline solution to No. 2; 0.5 c.c. to No. 3; 0.74 c.c. to No. 4 and 1 c.c. to No. 5.

Corpuscles are added the following day.

8. Mix the contents of all tubes gently but thoroughly and place in a refrigerator at 6 to 8° C. for 15 to 18 hours.

9. Warm the tubes in a water-bath at 38° C. for *five to fifteen minutes but not longer*\*<sup>21</sup> and add 0.5 c.c. hemolysin (carrying two units) to all tubes except the corpuscle control and reading scale; thoroughly mix the 2 per cent corpuscle suspension (which has been carried over in a refrigerator from the previous day) and add 0.5 c.c. to all tubes except those of the reading scale.

10. Add corpuscle suspension to the tubes of the reading scale as follows: 0.13 c.c. to No. 2; 0.25 c.c. to No. 3; 0.38 c.c. to No. 4 and 0.5 c.c. to No. 5.

11. Mix the contents of all tubes gently but thoroughly and place in a water-bath at 38° C. for one hour (the water must reach above the level of the contents in the tubes).

12. Place all tubes in a refrigerator for one to three hours to permit the partial settling of nonhemolyzed corpuscles; the degree of inhibition hemolysis is then read off and recorded for each tube with the aid of the reading scale as -, + (1), ++ (2), +++ (3), or ++++ (4). All serum controls, antigen and hemolytic controls should show complete hemolysis.

13. Tube No. 1 of the color scale shows a - reaction; tube No. 2 shows a +; tube No. 3 shows a ++; tube No. 4 shows a +++ and tube No. 5 shows a ++++ reaction.

Experience has shown that the reactions may be interpreted as follows:

*Very strongly positive* if there is partial or complete fixation of complement in the first four of all five of the fixation series.† Examples: 4431 -; 44421; 1442 -.

*Strongly positive* if there is partial or complete fixation of complement in the first three tubes. Examples: 441 - -; 421 - -; 241 - -.

*Moderately positive* if there is partial or complete fixation of complement in the first two tubes. Examples: 44 - - -; 41 - - -; 31 - - -.

*Weakly positive* if there is partial or complete fixation of complement only in the first tube. Examples: 4 - - - -; 3 - - - -; 1 - - - -.

*Negative* when all tubes show complete hemolysis. (-----.)

The following reactions with a syphilitic serum and spinal fluid show the method of recording and reporting: (Fig. 6.)

\*This preliminary warming may be omitted; if more than 15 minutes are used incomplete hemolysis may occur.

†Occasionally a serum will show less fixation of complement in the first tube carrying 0.1 c.c. serum than the second tube carrying 0.02 c.c. as a +, +++, +, - and - (control) reaction (recorded as 2, 4, 3, 1, -). It may be assumed that this is due to the presence of natural antisherp hemolysin but I have seen the phenomenon occur with hemolysin free sera and believe that it is due to the presence of other serum constituents in this relatively large amount of serum interfering with the fixation of complement by antigen and syphilis antibody. So far I have not seen this occurring with spinal fluids.

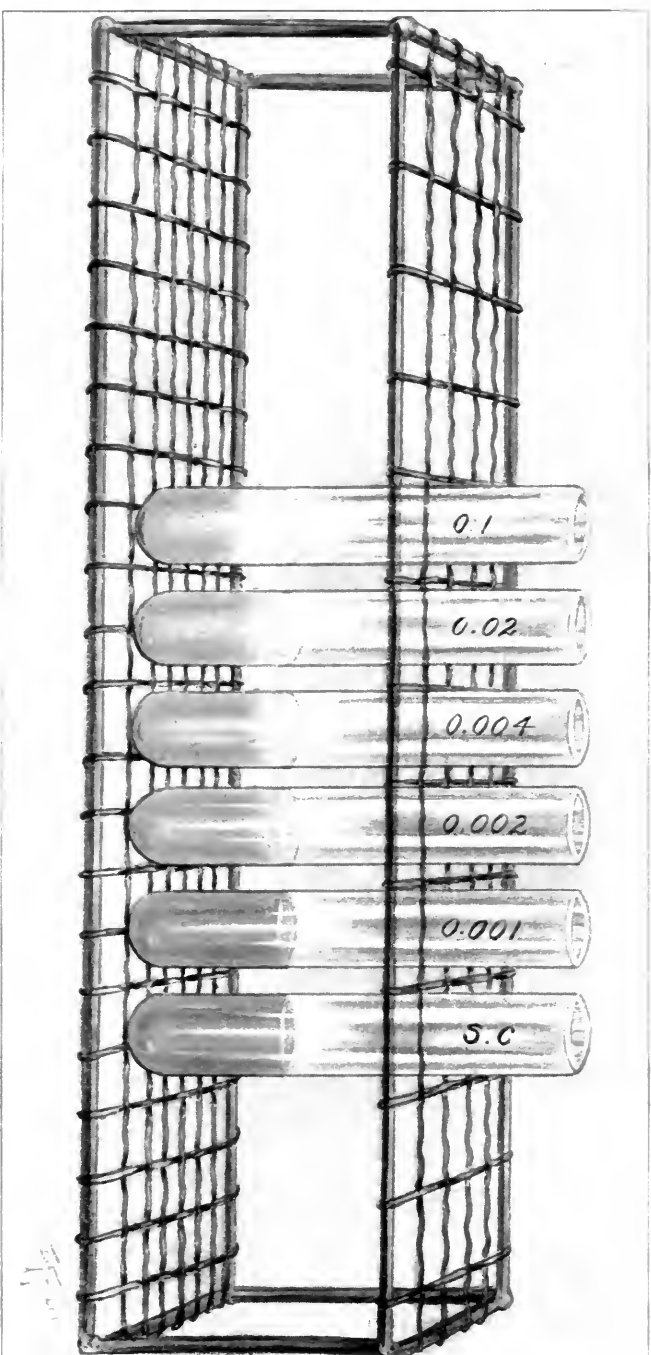


Fig. 6.—A positive reaction with the new complement-fixation technic. Shows test tubes and volume in each slightly reduced in size; also depth of color. The reaction is 4421 (very strongly positive).





## Quantitative Reaction.—Strongly Positive (4421 -).

Serum	0.1	c.c. =++++
"	0.02	c.c. =++++
"	0.004	c.c. =++
"	0.002	c.c. =+
"	0.001	c.c. =-
"	0.1 (control)	c.c. =-

## Quantitative Reaction.—Very Strongly Positive (4442).

Spinal Fluid	0.5	c.c. =++++
"	" 0.25	c.c. =++++
"	" 0.125	c.c. =++++
"	" 0.0625	c.c. =++++
"	" 0.03125	c.c. =++
"	" 0.5 (control)	c.c. =-

## THE QUALITATIVE COMPLEMENT-FIXATION TEST

The qualitative test is conducted in the same manner as the quantitative test except that two tubes instead of six are employed; otherwise the technic is the same and may be described more briefly:

1. For each *serum* arrange two regulation test tubes and place 0.8 c.c. saline and 0.2 c.c. serum in the first; mix the contents and transfer 0.5 c.c. to the second tube (control).

2. For each *spinal fluid* arrange two regulation test tubes and place 0.5 c.c. spinal fluid in each.

3. Add 10 units of antigen (0.5 c.c. dilution) to the first tube and 0.5 c.c. of saline solution to the second or control tube, of each series.

4. After waiting five to thirty minutes add 1 c.c. of diluted complement (carrying two full units) to both tubes of each set.

5. Set up antigen, hemolytic system and corpuscle controls as previously described; also a syphilitic serum and normal serum for a positive and negative reaction, as described above.

6. Set up first part of the reading scale as described with the quantitative test.

7. Mix the contents of all tubes gently but thoroughly and place all tubes in a refrigerator at 6 to 8° C. for 15 to 18 hours.

8. Warm the tubes in a water-bath at 38° C. for *five to fifteen minutes (not longer\*)*; add 0.5 c.c. hemolysin (2 units) to all tubes except the corpuscle control and reading scale. Gently but thoroughly mix the 2 per cent corpuscle suspension carried over in the refrigerator from the previous day and add 0.5 c.c. to all tubes except those of the reading scale.

\*This preliminary warming may be omitted; if more than 15 minutes are used incomplete hemolysis may result.

9. Finish the reading scale by adding corpuscles as previously described.

10. Mix the contents of all tubes gently but thoroughly and incubate in a water-bath at 38° C. for one hour.

11. Place the tubes in a refrigerator for one to three hours to permit the partial settling of nonhemolyzed corpuscles and read the results with the aid of the scale. All serum, the antigen and hemolytic controls should show complete hemolysis; the corpuscle control should show no hemolysis.

12. The results are read with the aid of the reading scale as previously described and recorded according to the + + + +, + + +, + +, + and - method of recording complement fixation in the first tube of each set:

- + + + + = strongly positive (100 per cent inhibition of hemolysis)  
 + + + = moderately positive (about 75 per cent inhibition of hemolysis)  
 + + = weakly positive (about 50 per cent inhibition of hemolysis)  
 + = very weakly positive (about 25 per cent inhibition of hemolysis)  
 - = negative (complete hemolysis)

#### SUMMARY

1. A new complement-fixation test for syphilis is described based upon the results of studies in the standardization of technic.

2. The new test is believed to have greatly increased the sensitiveness of the complement-fixation reaction in syphilis while possessing practical specificity and yielding no nonspecific reactions.

3. The new test also aims to fulfil the requirements of technical

TABLE VI  
THE QUANTITATIVE COMPLEMENT-FIXATION TEST FOR SYPHILIS

TUBE	PATIENT'S SERUM* IN 0.5 c.c.	ANTIGEN 10 units	COMPLE- MENT (2 full units)	Primary incubation at 6-8° C. for 15-18 hours followed by water-bath for 5 to 10 minutes.	HEMOLY- SIN (2 units)	CORPUS- CLES (2 %)	Secondary incubation 1 hour at 38° C. Read 1 to 3 hours later with scale.
1	0.1 c.c.	0.5 c.c.	1.0 c.c.		0.5 c.c.	0.5 c.c.	
2	0.02 c.c.	"	"		"	"	
3	0.004 c.c.	"	"		"	"	
4	0.002 c.c.	"	"		"	"	
5	0.001 c.c.	"	"		"	"	
6	0.1 c.c. (control)	-	"		"	"	
7	Antigen Control	0.5 c.c.	"		"	"	
8	Hemolytic Control	-	"		"	"	
9	Corpuscle Control	-	2.5 c.c. saline		-	"	

\*Spinal fluid doses: 0.5, 0.25, 0.125, 0.0625, 0.03125 and 0.5 c.c. (control).

TABLE VII  
THE QUALITATIVE COMPLEMENT-FIXATION TEST FOR SYPHILIS

TUBE	PATIENT'S SERUM* IN 0.5 c.c.	ANTIGEN (10 units)	COMPLE- MENT (2 full units)	HEMOLY- SIN (2 units)	CORPUS- CLES (2 %)	
1	0.1 c.c.	0.5 c.c.	1.0 c.c.	0.5 c.c.	0.5 c.c.	Secondary Incuba- tion 1 hour at 38° C. Read 1-3 hours later with aid of scale
2	0.1 c.c. (control)	-	"	"	"	
3	Antigen (control)	0.5 c.c.	"	"	"	
4	Hemolytic (control)	-	"	"	"	
5	Corpuscle (control)	-	2.5 c.c.	-	"	
Wait 5-10 minutes			Primary Incubation 15-18 hours at 6-8° C. followed by water-bath for 5-10 minutes.			

\*Spinal fluid used in dose of 0.5 c.c. in both tubes.

simplicity, accuracy, and economy and to yield uniform results in different laboratories.

4. The new test yields an accurate quantitative measure of complement fixation in syphilis of value as a serological guide to treatment; a qualitative test is also described.

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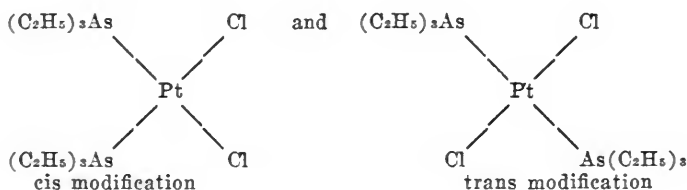
# SILVER SALVARSAN, QUALITATIVE AND QUANTITATIVE STUDIES

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(Received for publication, August 17, 1921)

THE widespread use of "Silver Salvarsan" has given an impetus for detailed study of one of the most interesting chemical compounds available for clinical and chemical investigation. Its peculiar physical and chemical properties have served to attract the attention of many investigators and its clinical application has shown it to be a very potent biological agent in the treatment of syphilis.

Cahours (1870) and Gal observed that when platinic chloride was added to triethyl arsine drop by drop, there was a reduction to the platinous condition with the formation of two stereo isomeric compounds (cis and trans).



These isomeric compounds were in accord with the Werner coordination theory. Other heavy metals behaved in somewhat the same manner further emphasizing the theory of residual affinities.

In the course of the researches carried out in the Ehrlich laboratories, Bertheim, Benda, Kahn, Karrer and more recently Kolle and his collaborators, Binz, Bauer and Hallstein studied the interaction of arsenoaryl compounds and various metallic salts. They synthesized a new series of coordination compounds in which different molecular proportions of the heavy metal salts enter into intimate combination with the arseno compounds. The complex metallic arsenoaryl derivatives hold the metal in a nonionizable condition such that all ionic manifestations from an analytical point of view

are entirely masked. The formation of these metallic complexes is a very general one and applies to all trivalent compounds of arsenic irrespective of the degree of substitution in the ring. The tendency for forming these metallic complexes is less pronounced in the case of the single ring trivalent arsenic preparations ( $R.AsO$  and  $R.AsH_2$ ). In the case of the arsenoxides the residual affinity of the arsenic seems much weaker, being particularly influenced by the "Kernsubstituenten."

This series of investigations took more definite form when Ehrlich publicly made these discoveries known at the International Congress of Medicine held in London in 1913, the first patents appearing in the fall of 1912. A short time afterward, Danysz (1913, 1914) working independently announced the discovery of metallic complexes from salvarsan and silver nitrate.

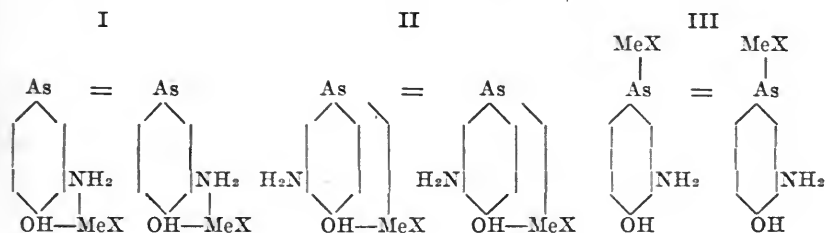
Ehrlich and Karrer (1915) published a more detailed communication of the results of their work describing their product which is not of the same composition as the product now being successfully used in the treatment of lues. The discussion of the chemical structure of the compound is given in the following paragraphs. It is given in detail inasmuch as Binz, Bauer and Hallstein suggest an entirely different constitution. This compound is of extreme interest because it is formed by the action of an oxidizing substance in the presence of a strong reducing product. However, when the substances are molecularly controlled the metallic complexes are formed without violent chemical reaction.

Ehrlich and Karrer (1915) found that aromatic compounds of trivalent arsenic formed complex salts with heavy metals which were characterized by their intense color and great stability. The application of these observations included first, all arseno compounds, and, under certain conditions, arsines and arsenoxides, second, all salts of copper, silver, gold, mercury, palladium, platinum, iridium, ruthenium, and osmium. On account of the pharmaceutical interest of these preparations their chemical investigations were made and described under the additive metal compounds of 3-3' diamino, 4-4' dioxy arsenobenzene. The statements they make in regard to this compound apply *mutatis mutandis* to all other arseno derivatives. The striking phenomena are observed when a few drops of silver nitrate are added to salvarsan dissolved in methyl alcohol.

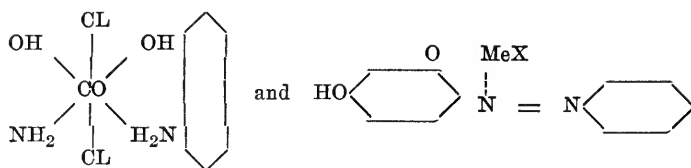
Finally, a reddish brown color is observed, but not the slightest trace of silver chloride is found. No silver "ions" can be determined in the solution and as far as analytical results are concerned, the silver salt has disappeared from the solution. An interesting phenomenon is observed if gold chloride is used in the same way as silver. The reddish brown color appears and gold ions disappear from solution. However, if an excess of gold solution is added a heavy precipitate of metallic gold is formed. If the precipitate is filtered off and the filtrate is examined, no trace of an arseno compound is found but instead arsenic acid is obtained. These compounds show less inclination for crystallization than the arseno compounds and consequently there is less opportunity to study their uniformity and purity. (A discussion of the physical chemical phenomena will be found later.) By actual titration it was found that the theoretical amount of gold which could be held in the complex corresponded exactly to two molecules and that an additional amount started oxidation of the coordination compound into the corresponding arsenic acid.

Other metals were used and the question of residual valency was studied. In the general discussion they state: "dioxy diamino arsenobenzene has two residual valencies and can therefore add a maximum of two molecules of a metal salt. The magnitude of the residual affinity of the metal salts seems to be of minor importance."

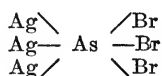
Three views of the constitution of these metal compounds are possible according to the Ehrlich-Karrer theory. First, it can be assumed that the metal is bound by the ortho-amino phenol group (I), secondly that it is bound by both the phenol and arseno groups (II), and finally that the residual affinity of the arseno group holds



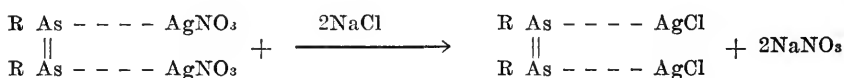
the metal. The foregoing ideas are based upon analogous compounds such as described by Metzler (1910), and Moehrlau and



Steimig (1904). Formula III was finally decided as representing the structure of the complex. In confirmation of this idea the theory of Hipfert and Herrmann (1913) is utilized in which they found compounds with this formula:



It is interesting to note in this particular instance that the arsenic in this case has three residual valencies. In the single ring compounds (arsenoxides) the residual valency is found to be much weaker and in those of the arseno type one molecule of the metal salt may be substituted. In preparing the metal complex, the arseno compound is dissolved in methyl alcohol and combined with a methyl alcohol solution of the desired metal salt, precipitating the resulting solution in ether. For example:



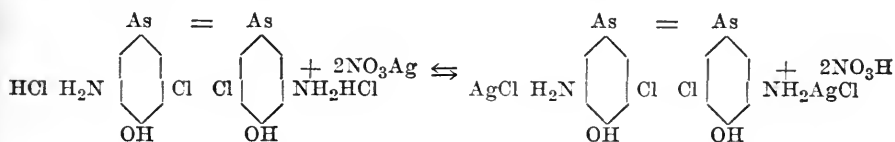
Danysz (1913, 1914) independently studied some arsenicals in conjunction with heavy metals. It was found that a certain number of parasites became accustomed to the products which were intended to destroy them in the diseased organism and for this reason the idea of using simultaneously or successively other active products was suggested. Laveran used trypan red and arsenious acid; Laveran and Thiroux associated atoxyl with orpiment; Moore, Nerenstein and Todd employed atoxyl with mercury salts; Morgenroth and Tugendreich studied salvarsan with ethyl hydrocupreine and salicylic acid. These combinations suggested to Danysz the use of active combination products. The attempt of Danysz in this instance was to combine various active products in order to associate in the same molecule the selective affinity of the one with the anti-septic power of the other.



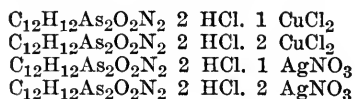
In the first paper the "arseno-argintique" combination is reported without any formula. The biological results were given in considerable detail. In the second paper the method of preparing the product is described. He also stated that he worked independently of Ehrlich on these metallic combinations. Danysz found these compounds to have the disadvantages of being highly colored and containing an energetic oxidizing element (nitric acid). The method of preparation consisted in dissolving the iodide and bromide of silver in potassium cyanide and then adding this drop by drop to a solution of the arseno compound. Hydrocyanic acid gas is evolved in this process; the precipitate is redissolved with hydrochloric acid. One molecule of silver salt is used for each molecule of arseno compound. The solution is precipitated and dissolved in water slightly alkalized with sodium hydrate. Mercury, gold and platinum salts were found to be less stable. The sterilizing power "in vitro" and "in vivo" was found to be considerably greater for this silver preparation than for the corresponding dioxo diamino arsenobenzol. These coordination compounds were extended and antimony was added, yielding the product under the trade name luargol.

These compounds were further studied by Danysz (1914 *b*) in relation to their sterilizing properties and their action on normal blood and specific serums. He concludes that the silver salts possess a greater parasiticide power in proportion to their toxicity and modify the normal properties of blood and serum to a smaller degree than other preparations. Dilutions of 1:1000 have no appreciable action on the elements of the blood, and no cases of poisoning were observed.

After the death of Ehrlich, Binz, Bauer and Hallstein (1919 *a*) working with Kolle continued the investigations on the constitution of silver salvarsan. They attempt to prove their point by using a dichlor-salvarsan which is treated with silver nitrate.

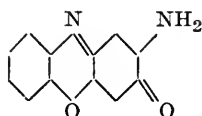


Karrer (1915) and Ehrlich pointed out that salts of the following type were formed with the discussion above.



etc.

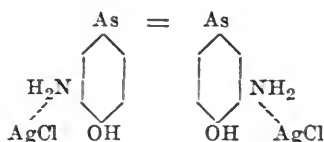
Analysis of products of this nature offers an objection due to the character of the reaction in which an easily oxidized salvarsan is treated with metallic salts possessing strong oxidizing possibilities. It is possible that at least a small quantity of the salvarsan is oxidized in at least three places in its structural formula inasmuch as the corresponding amino oxy phenyl arsinic acid is easily isolated, and it is often observed that the amino phenols are responsive to mild oxidizing agents involving both the amino group and the hydroxy group. The change in the amino group may give rise to the colored product.



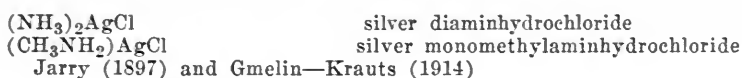
With these ideas in mind the dichlor salvarsan was used as a starting point and this product was treated with the various metallic salts in order to determine the quantity and the point of coordination of these metallic derivatives.

In the previous communication Binz, Bauer and Hallstein stated that the position of the metal salts in the complex formation of the salt molecule remained open. In the following paper they believed that sufficient and satisfactory proof was offered to disprove the theory of Karrer and to establish another through the use of tetra-brom-arsenophenol sodium as this product contained no amino group. When silver nitrate acts upon this compound, a disilver tetra-brom-arsenophenolate is formed, a corresponding reaction takes place with copper salts. If this silver phenolate is treated with caustic soda, a clear brown solution is formed, the same as in silver salvarsan sodium. However, the Bechold ultrafiltration method established the presence of colloidal silver, the arsenic radical having been split from the nucleus (Benda, 1911). In the silver salt a clear solution is formed with caustic soda. This observation was believed to indicate that the metallic salt was not attached to the arseno group or the phenolic group as suggested by Karrer

but possessed some linking to the amino groups, the residual valencies offering sufficient explanation as

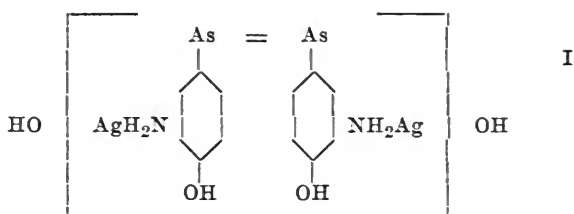


The aliphatic and aromatic amines show analogous conditions as:

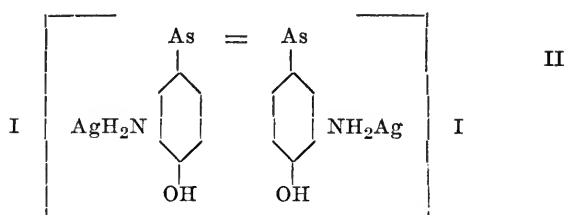


The general behavior of this aromatic metallic complex is remarkable in the presence of a strong oxidizing agent in view of the fact that it possesses two ortho amino groups as well as an easily oxidizable arseno group. It is possible that intermediate silver compounds are formed as an excess of silver salts liberates metallic silver. Earlier observations gave rise to the view that alkaline silver salvarsan solutions produced a silver mirror proceeding from the surface toward the bottom according to the progress of oxidation while a silver mirror is generally a result of reduction. The plausible explanation is due to an oxidation of the arseno group yielding amino-oxy-phenyl-arsenoxide which in turn can no longer hold the complex silver oxide.

The analogy of silver diamin hydroxide  $(\text{NH}_3)_2\text{Ag} \text{OH}$ , an instance of a complex cation and a simple anion, affords a preliminary suggestion for the structure of the silver salvarsan base:

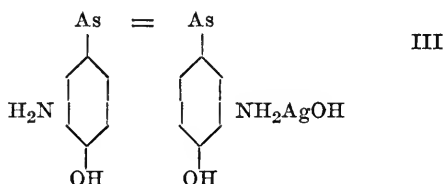


That such a combination is possible has been proved by the addition of silver nitrate to a solution of dioxy diamino arsenobenzol iodine hydrate giving a complex iodine Ag salt:



The iodine atoms are present as anions and the organic arsenic radicals as cations. The iodine is split off quantitatively by the use of dilute caustic. If the iodine is split off in this manner, a product the same as I should be formed and such is the case (brown amorphous substance insoluble in water).

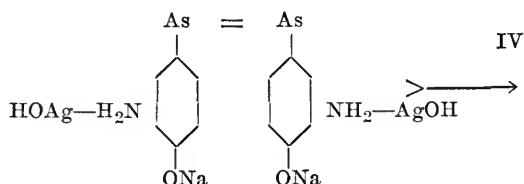
The commercial silver salvarsan contains only one atom of silver to two atoms of arsenic and in the primary analysis would be represented by the formula:

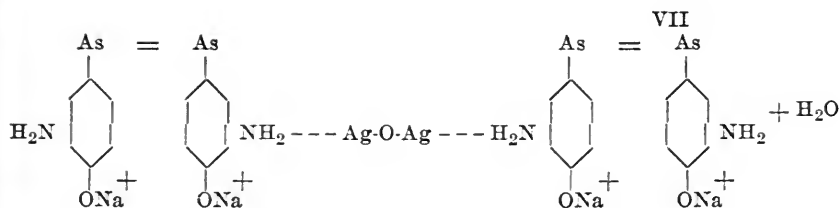
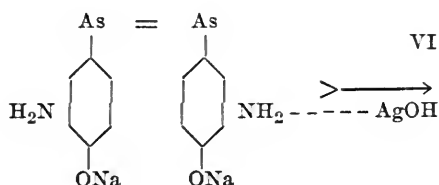
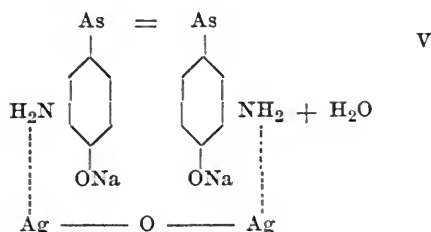


Formulae I and III show the two possible types of silver complexes using one and two atoms of silver. The formation of the silver salt takes place and anhydridization must then follow. This is true to type:

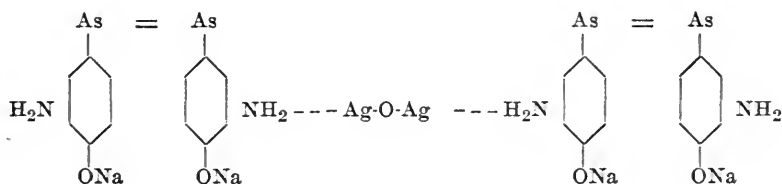


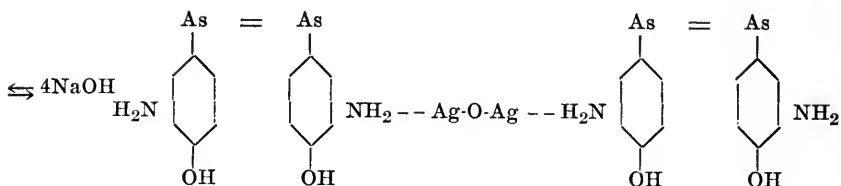
Its application with the formation of the sodium salt is represented by the four following formulae:





These last formulae can be regarded as an explanation of the change in color from brownish red to a characteristic dark brown which is observed upon the addition of caustic soda to the reaction mixture of salvarsan and silver nitrate. Further substantiation of these formulae is found in the electrolytic dissociation of the complex in which there are four (4) positively charged sodium ions and the negatively charged complex ion. Finally, the scheme of hydrolytic dissociation indicates:





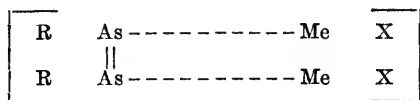
The experimental proof and analytical data are sufficiently convincing to show that silver is unmistakably in the nonionic form and that the compound is a silver oxide complex of simple proportions or an aggregate of molecules (polymerization) as indicated by its physical and biological manifestations which agree essentially with the suggestions of Sherndal and Myers regarding the physical nature of the arseno compounds.

#### AUTOOXIDATION OF SILVER SALVARSAN SODIUM WHEN STANDING IN SOLUTION

A peculiar feature of the product is its power of autooxidation indicating an intramolecular change giving rise to a less stable modification. If 3 g. of silver salvarsan sodium is dissolved in 150 c.c. of water and allowed to stand for 4 weeks in a closed bottle filled with nitrogen, a dark brown sediment is formed. The precipitate is separated by centrifuging from the solution which is colored only a light brown. Yield 1.17 g. of sediment.

The fluid which had been separated by centrifuging yielded 1.50 g. of dry residue; 0.3046 g. of this, upon decomposition with hydrogen peroxide, etc., gave 0.1267 g.  $\text{As}_2\text{O}_7$ ,  $\text{Mg}_2$ , on the other hand no silver chloride was obtained from the solution.

Karrer (1919) does not accept the views advanced by Binz, Bauer, and Hallstein and reiterates his previous statements on constitution, still adhering to the idea that the metal is directly anchored to the arsenic atoms as illustrated in the general formula:



Binz, Bauer, and Hallstein pointed out in the previous article that silver was held to the arseno complex by means of the salt forming amino and hydroxyl groups. They based their opinion on the fact

that "arsenobenzol (base) suspended in water does not add metal salts, and secondly that in the case of tetra-brom-arseno-benzol, precipitates could be obtained on the addition of such excess of silver salt that di-brom-phenol-arsinic acid was formed by oxidation."

In reply Karrer states: "I would again refer to the fact that in the reduction of phenyl arsinic acid and copper chloride with hypophosphoric acid, a red brown combination is formed which according to its origin and properties must be an arseno compound, and which contains copper bound in a complex form. This observation alone would be sufficient to affirm my opinion according to which the metal is bound to the arsenic. But I have also determined that other arseno compounds, as arsenophenylglycin, neosalvarsan, diamino-arsenobenzol, can form metal complex salts." (D.R.P. 270, 257, 258, per C. N. M.)

"I do not believe that the formulas which I have given for arseno metal complex salts require any change. They enable the intelligent explanation of all properties of the arseno metal complex salts. According to this formulation the arseno metal complex salts belong in the large class of complex combinations with a negative central atom, of which A. Werner speaks in a special chapter on *New Viewpoints in Organic Chemistry*" (3rd edition, page 300).

Binz, Bauer, and Hallstein, (*Ber. d. deut. Chem. Ges.*, 1920, liii, 416) essentially restate the same information found in earlier publications.

In the course of the biological investigations of the salvarsan group, Bauer (1919) made an extensive study of physical chemical condition of the aqueous solutions of salvarsan and its related derivatives. The classical method of Graham using diffusion phenomena was tried on these salts and they were arranged in a well-defined series showing distinct differences in physical properties. The experiments were chemically controlled. Ultramicroscopic studies were conducted, and, in addition, the ultrafiltration method of Bechold was applied to these substances, thereby giving direct proof of the variability in the size of the particles using controls with a molecular weight from 2400 to that of hemoglobin about 16000. The chemist working on the subject of arsenic combinations is often presented disagreeably with the uncomfortable way in which these substances dissolve, often giving a gelatinous product offer-

ing many difficulties for filtering and washing and clinical use. On this account it is interesting to study these combinations from a physical standpoint. As a result of numerous experiments it is definitely pointed out that these arsenic combinations do not act as genuine colloids but on the other hand diffuse more slowly than crystalloids.

Observations with the ultramicroscope show a field oftentimes filled with numerous particles and actively movable.

In the ultrafiltration apparatus, a collodion filter with 6 per cent glacial acetic was used. It was impermeable to tincture of litmus and hemoglobin.

It was shown that in alkaline solutions of salvarsan, the size of the particle varied according to the method of preparation.

After considerable study, Bauer arranged the arsenicals in the following table, beginning with the ones that diffuse more slowly:

1. Collargol
2. Silver salvarsan sodium
3. Neosalvarsan
4. Salvarsan dihydrochloride
5. Freshly alkalinized salvarsan
6. Salvarsan sodium (ampuled powder)
7. Atoxyl
8. Silver nitrate

These diffusion experiments give us very clearly an illustration as to how we can picture the action of the substances observed in the organism. We must suppose that the sodium salts of the salvarsan group are hydrolyzed in the organism and thus are transformed into the free compounds which are then precipitated in colloidal form through the presence of protein which acts as a protective colloid.

In these experiments Bauer points out that silver salvarsan should be considered chemically as a homogenous substance in which the silver is held in complex combination.

In arriving at the constitution it was necessary to carry out many analytical determinations and it was important to cautiously break up the product for actual determination of the arsenic and silver in the compound. In order to do this, Binz (1919) devised a method for analyzing silver salvarsan. The method is as follows:



0.6232 gram of "silver salvarsan" is heated to boiling for one hour with 30 cubic centimeters of water and 6 cubic centimeters of perhydrol (30 per cent  $H_2O_2$ ). The brown color completely disappears and the silver separates out as the oxide together with metallic silver (possibly). The mixture is evaporated to dryness on the water-bath with 9 cubic centimeters of concentrated nitric acid. A small part remains as silver chloride due to sodium chloride in the product. The dried residue is then treated with 30 cubic centimeters of hypochlorite solution which is prepared as follows. Eleven cubic centimeters of water and 84 cubic centimeters of hydrochloric acid (s. g. 1.19) are mixed. Eighty-five cubic centimeters of this mixture is allowed to act on 13 grams of potassium permanganate and the chlorine collected in 60 c.c. of a 10 N sodium hydrate and 150 c.c. of water. One cubic centimeter of this solution corresponds after the addition of potassium iodide to about 1.5 cubic centimeters of tenth normal thiosulphate. The residue is refluxed with vigorous boiling for one hour, thereby converting all of the silver into chloride and splitting off the arsenic. The excess of hypochlorite is removed by boiling with 10 cubic centimeters of hydrochloric acid, using the reflux to avoid any loss of arsenic. The contents of the flask are poured into a beaker and diluted with water. The silver chloride is collected on a tared Gooch crucible and weighed. The arsenic is determined as magnesium pyro arsenate.

Perhydrol is not available and for that reason it was impossible to repeat the work of Binz. In addition the method is somewhat long for a routine application.

In order to overcome these difficulties the following methods were devised in order to obtain an accurate and rapid routine analytical procedure. All methods were carefully checked against the complete gravimetric analyses. Analyses marked with "G." indicate gravimetric determination throughout. Nearly all of the silver determinations were gravimetric.

*Method I.*—Accurately weigh out about 0.2 gram of "silver salvarsan" in a 300 c.c. beaker. Add 10 cubic centimeters of distilled water to completely dissolve the product. To this 5 cubic centimeters of normal sodium hydrate are added in order to aid the oxidation which is to be accomplished by means of hydrogen peroxide. Cautiously add 100 c.c. of commercial hydrogen peroxide.

Heat on the water-bath for one hour. The silver oxide will be precipitated as a very fine powder. Sometimes the remaining solution is slightly colored showing incomplete oxidation of the phenyl arsenic acid with possibly a small quantity of colloidal silver. Remove from the water-bath and filter through a good grade of quantitative paper. If the silver particles pass through the paper it may be necessary to add sufficient acetic acid to neutralize the solution. This will coagulate the silver and there is a slight danger of occluding a small quantity of arsenic with the silver and for this reason it is advisable to break up the larger particles before filtration. The silver oxide is carefully washed with warm distilled water. Carefully remove the precipitate from the funnel, and place the spread out paper on the bottom of a beaker. Add 5 c.c. of concentrated nitric acid and digest for ten minutes on the water-bath. Unless the paper has been carefully spread out on the bottom of the beaker, some of the silver oxide will fail to dissolve, but if care has been followed in spreading the paper out no difficulty will be experienced. During this digestion on the water-bath, the excess of nitric acid is driven off and the filter paper is partially digested. Now add 20 cubic centimeters of hot distilled water, heat for a half hour longer on the water-bath. Filter and wash with hot water. When the solution is cool, add 10 cubic centimeters of concentrated nitric acid and 1 cubic centimeter of saturated ferric ammonium sulphate solution. Titrate with carefully standardized tenth normal potassium sulphocyanide calculating the silver from this value.

The filtrate from the silver oxide precipitation is now treated according to the Lehman method for arsenic described by Myers and DuMez (1918).

The alternative method was used in this investigation in which the dissolved silver oxide was treated as described above and collecting the silver in the form of silver chloride by adding 5 cubic centimeters of normal hydrochloric acid. Collect the precipitate in a tared Gooch crucible.

*Method II.* Place about 0.2 gram of silver salvarsan, accurately weighed, in an Erlenmeyer flask, and carry out the Lehman process, for the determination of arsenic as described by Myers and DuMez. At the point of digestion and while the solution is hot, cautiously add 5 cubic centimeters of normal hydrochloric acid in order to obtain the precipitation of silver chloride. Dilute the solution with

50 cubic centimeters of distilled water. Filter off the silver chloride through a tared Gooch crucible, wash thoroughly and dry the precipitate in the usual manner. Weigh and calculate the percentage of silver from the amount of silver chloride.

The filtrate is concentrated and the arsenic content is obtained by means of the modified Lehman process.

These methods agree with the gravimetric determination of arsenic and silver and furnish a rapid and accurate routine method for examining the compound. Table I shows the results obtained by the application of these methods by different individuals and different laboratories.

TABLE I  
ANALYSES "SILVER SALVARSAN"

CONTROL NUMBER	AS CONTENT IN PER CENT	AG CONTENT IN PER CENT	ANALYST
F.J.H. imported	20.6	14.00	M
	20.9	13.80	
F.D.L. imported	21.58	13.17	M
	21.40	13.40	
I	20.88	14.70	H
	20.80	15.10	
II	21.10	14.40	M
	21.00	14.56	
	20.95	14.45	
	21.20	14.30	
	20.80	15.10	
III	20.90	.....	L
	21.30	14.89	
	21.20	14.85	M
	21.30	15.12	
	21.10	15.05	
	(21.07 g.	14.80) g.	
	(20.87 g.	14.65) g.	
	21.23	14.86	
	20.87	15.20	
	21.36	14.72	S
	21.27	14.78	
	.....	15.00	
IV	21.00	14.50	L
	20.60	.....	
	20.20	14.20	L
	20.20	14.20	

TABLE I—( CONTINUED )

CONTROL NUMBER	AS CONTENT IN PER CENT	AG CONTENT IN PER CENT	ANALYST
V	20.50	14.33	M
	20.60	14.27	
		15.10	L
		15.15	
	19.08 g.	15.72 g.	M
VI Incompletely dried	19.08 g.	15.41 g.	
	19.26	15.14	
	19.60	15.72	
	18.60	14.80	L
	18.87	15.72	M
	19.08	15.41	
	19.08 g.	15.41 g.	
	18.96	15.41	S
	19.03	15.47	
	19.09	15.50	
VII	19.64	13.67	H
	19.57	13.30	
	19.30	13.80	
	19.28	13.88	
	19.60	13.85	
VIII	19.43	14.20	H
	19.29	14.12	
	19.35	14.10	
	19.95	13.85	
	19.50	13.80	
IX	19.62	13.80	H
	19.47	14.10	W
	19.65	14.40	L
X	.....	14.50	H
	19.31	14.30	W
XI	18.70	14.00	L
	19.40	14.67	H
	19.04	14.04	W

In Table I it is observed that the analytical results agree very uniformly. The comparisons are the result of analyses in three different laboratories and five operators. The table is really divided in two sections: One section deals with a product whose Ag-As ratio was intended to be 15:21. The second section deals with a

product in which the ratio should be 14:20. Method II was generally used in these determinations. The silver was occasionally obtained by Method I and then titrated with potassium sulphocyanate. The arsenic was determined in a few instances gravimetrically following the procedure of Myers and DuMez (1918). The agreement is excellent in most instances and as a routine Method II seems to give satisfaction.

#### QUALITATIVE TESTS

“Silver salvarsan” is the completely alkalized mono silver salt of salvarsan. “Silver salvarsan” is a brownish black powder, unstable in moist air, and moist air containing carbon dioxide. The slight changes in color are due to the state of physical aggregation of the particles. It is readily soluble in cold water giving a slightly alkaline reaction and an ichthyol brown solution (distinction from salvarsan and neosalvarsan).

The solutions used for the qualitative tests described below are in all cases the usual (T. S.) used in qualitative chemical analyses unless otherwise stated. The silver salvarsan solution is prepared by dissolving 1 gram of salt in 500 cubic centimeters of *cool* distilled water. The letters SS indicate the above solution.

Dilute sodium hydroxide when added to SS produces no immediate change (distinction from arsphenamine). If it is exposed to air or oxygen, a silver mirror forms at the surface, gradually proceeding downward (distinction from neosalvarsan and salvarsan).

Sodium carbonate solution added to SS produces no precipitate.

Sodium carbonate solution (saturated) added to SS produces no precipitate.

Sodium bicarbonate (saturated) solution added to SS produces a brown precipitate of a complex salt.

Dilute hydrochloric acid cautiously added to SS produces a brown precipitate (distinction from salvarsan and neosalvarsan (yellow precipitate). This precipitate dissolves with the addition of more acid. Gently warming, no irritating odor of sulphur dioxide is obtained (distinction from neosalvarsan).

Concentrated hydrochloric acid produces a brown precipitate when added to SS, insoluble in excess, changing into a greenish yellow precipitate.

Dilute sulphuric acid added to SS produces a precipitate insoluble in a slight excess of acid.

Concentrated sulphuric acid added to SS produces a precipitate readily soluble in an excess of acid.

Dilute nitric acid when added to SS produces a brown precipitate dissolving in an excess of reagent.

Concentrated nitric acid when added to SS produces a temporary precipitate readily soluble in excess.

Acetic acid when added to SS produces a brown precipitate of base slightly soluble (distinction from salvarsan).

Potassium permanganate when added to SS produces a precipitate which evolves ammonia when heated on account of the alkaline nature of the compound.

Hydrogen peroxide when added to SS produces a precipitate in the cold (distinction from salvarsan and neosalvarsan).

Dilute sodium chloride when added to SS produces no precipitate when acidified with sufficient nitric acid.

Saturated sodium chloride when added to SS salts out the product. The use of sodium chloride shows the absence of ionizable silver.

Bromine water when added to SS produces a reddish coloration and a precipitate. The color disappears with an excess of the reagent. The precipitate is soluble in alkali.

The alkaloidal reagents all produce a precipitate when added to SS.

Phosphotungstic acid produces a reddish precipitate when it is added to SS.

Phosphomolybdic acid when added to SS produces a reddish brown precipitate.

When sodium carbonate is added to either of the above solutions, a dirty green color is formed.

Picric acid when added to SS produces a yellow precipitate.

Ferric chloride when added to SS produces a reddish colored solution, an excess of reagent causing a precipitate.

Binz (1919) states: "In conclusion an observation may be made which has indeed no bearing on the analysis of silver salvarsan, but which may come into consideration in the question which is still to be cleared up regarding the constitution of silver salvarsan sodium. If silver salvarsan sodium is properly treated with reducing agents instead of with oxidizing agents, the silver is likewise

separated from the molecular association. Strange to say, however, this takes place only in the presence of air:

Two-tenths grain of silver salvarsan sodium is dissolved with 0.34 g. sodium hydrosulphite in 5 c.c. normal solution of caustic soda and allowed to stand overnight in a test tube with a soda lime tube attached. On the following morning a circular silver mirror appears on the surface of the fluid, which in the course of several days advances into the mass below as the atmospheric oxygen penetrates. If the reaction vessel is filled with nitrogen, no silver at all is observed. The silver also appears after a much longer time if upon the admission of air the amount of hydrosulphite is increased to 1.7 g. and thus the action of oxygen is delayed. The amount of metallic silver given off is less than that contained in the substance, and probably a part is combined in the form of a black precipitate with one of the arsinic acids formed by the oxidation.

The results of these experiments can be conclusively determined only when the constitution of silver salvarsan sodium is cleared up beyond objection. Meanwhile it may be imagined that silver, similarly as in the above mentioned analyses, with hydrogen peroxide, is separated by atmospheric oxygen as silver oxide and is then first accessible to the action of the reducing agent.

#### SUMMARY

1. A brief review of the chemical literature is given for the purpose of showing the two prevailing ideas as to the constitution of this important drug.

2. The product described in this discussion is the sodium salt of the mono silver-3-3'-diamino-4-4'-dioxo-arseno-benzene.

3. The analytical methods applicable to this compound are given with a table showing the uniformity of analyses in different laboratories when these methods are used.

4. The qualitative tests for identifying the product are included in the discussion.

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## ALOPECIA SYPHILITICA GENERALISATA WITH A REPORT OF A CASE

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(Received for publication, July 25, 1921.)

COMPLETE syphilitic alopecia is a rare condition. Most textbooks on dermatology as well as those dealing exclusively with syphilis pass the subject over either without mention or with the statement that the condition is unusual.

Thompson<sup>1</sup> states in his textbook on Syphilis that such is the case. He however quotes Abraham and Davis in Power and Murphy's System of Syphilis that "more cases than one" of complete syphilitic alopecia have come under their care.

Thompson also quotes a case of Chalmers which was presented before the Toronto Clinical Society in 1900. This patient was a female, twenty years old, in whom the hair began to fall at the age of five and again at twelve. She was treated for interstitial keratitis two years previous to the time of presentation at which time there were but two hairs on the body, these being located on the anterior portion of the scalp.

Thompson's own case was originally reported in 1916. This case was a male of twenty-three who had had a chancre of the penis two years and a half previously. The hair of the eyebrows began to fall out two weeks after the appearance of the chancre, following which the hair of the other region began to fall out and in two months the body was entirely denuded. Vigorous treatment in this case failed to stimulate the growth of hair.

No mention of other cases of complete syphilitic alopecia can be found in the literature, which makes it seem advisable to report the following case at this time.

The similarity of the case reported by Chambers to my case is worthy of mention, in that the loss of hair seemed to come at intervals of five or six years.

O. K. J., male, aged 26. Came to me for treatment on April 10, 1920. Father, mother, brothers and sisters in good health, and baldness is not char-

acteristic. Past history of patient, ordinary diseases of childhood, no history of any eruptions at any time in life, no scars or marks of any kind that would indicate syphilis. At the age of six years the patient lost all the hair of his head, the scalp being left as smooth as ivory. After a period of six months to a year the hair came in again, apparently as thick as before. Again at the age of twelve the entire head of hair was lost, and at this time some "hair restoratives" were used but, with what result it would be difficult to say as the hair grew again after a variable length of time. At the age of eighteen the hair of the head again fell out, and at this age the hair from the axillae, eye brows, eyelashes, pubes and legs also was lost, not a hair remaining on the body. This was the condition of the patient when he came to me for treatment eight years later. During all this period he remained in good physical condition, and had no treatment except some local applications to the scalp. I might say also that the patient was accepted by the draft board and served his country during the late war, and while his head was as smooth as a billiard ball, the true condition was apparently not suspected while in the army, or at least it was not mentioned. This patient was extremely anxious to get his hair back and I am quite sure withheld none of the essential facts in the case. Patient states that at no time was there any eruption or sores on the skin, but he does remember of having had a sore on the free margin of the tongue, which he thought was due to a roughened tooth; however, the sore on the tongue did not appear until some years after the hair fell out for the first time.

After a very painstaking physical examination in which I found absolutely no signs of syphilis, I suggested that a specimen of blood be taken and a Wassermann test made, to which he very readily submitted. The Wassermann proved to be a four-plus, and treatment was instituted at once. On the 19th day of April, 1920, the patient was given 0.9 gram of neoarsphenamine, the same dose being repeated every sixth day. In addition to the arsphenamine potassium iodide was given internally to the point of saturation.

The neoarsphenamine was given intravenously until six doses were taken, at which time all treatment was discontinued for a period of eight weeks.

At this time a second Wassermann was made, which showed a two-plus, which was very gratifying to both the patient and myself. Treatment was again resumed and given exactly as before until six doses of neoarsphenamine were given. Treatment was discontinued at this time for a period of three months, after which a Wassermann was made which showed a negative reaction. To complete the treatment two more doses of neoarsphenamine were given at monthly intervals.

The patient was left on potassium iodide for two months longer

at the end of which time all treatment was discontinued. The patient has been kept under observation for a year, during which time he has shown five negative Wassermanns, the last of which was made July 25, 1921.

The patient at this time has a full head of hair, in fact, the axillae, pubes, eyebrows, eye lashes, legs, etc., are covered with a full growth of hair.

#### REFERENCES

- <sup>1</sup>Thompson, Loyd: Syphilis, Philadelphia and New York, 1920, p. 111.

# Abstract of Current Syphilis Literature

It is the purpose of this JOURNAL to review so far as possible all literature on syphilis as it appears in other medical periodicals and to present it in abstract form. Authors are requested to send abstracts or reprints of their papers to the Associate Editor, Dr. Grayson E. Tarkington, Dugan-Stuart Bldg., Hot Springs National Park, Ark.

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GRAYSON E. TARKINGTON, M.D., EDITOR.

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**A. Study of the Incidence of Hereditary Syphilis.**—P. C. Jeans and J. V. Cooke, St. Louis, Mo. *American Journal of Diseases of Children*, 1921, vol. xxii, p. 402.

A study of the placenta and the Wassermann reaction on the cord blood was made on a series of 2,030 unselected infants in St. Louis. By examining the blood of 389 of these infants after 2 months of age it was determined that the proportion of cases of hereditary syphilis that could be certainly diagnosed by placental examination alone was 27 per cent while from the Wassermann reaction on the cord blood, 63.6 per cent of the cases could be recognized. By applying these two methods to the entire series the number of cases of hereditary syphilis in the whole group was determined. The incidence of hereditary syphilis established by this method is 15 per cent in the colored race, 1.8 per cent in the poor of the white race and less than 1 per cent in the well-to-do social classes. By applying these figures to the entire population of St. Louis it is estimated that the incidence of hereditary syphilis at birth in this city is 3 per cent, of which the colored population, although only 9 per cent of the total, contributes approximately half the cases.

**Syphilis and Infant Deaths.**—Millard Knowlton, Raleigh, N. C. *Public Health Reports*, 1921, xxxvi, p. 2305.

It is important that adequate medical service be available in all parts of the state. There should be enough medical practitioners with special knowledge of the diagnosis and treatment of syphilis so distributed over the state as to be accessible to all infected persons. When one member of a family is found to be syphilitic, it is desirable to have other members of the family examined for possible syphilis. This should apply to both old and recent infections where there has been a possible chance for transmission of the disease either by contact or inheritance. So much emphasis has been placed on the Wassermann test that the public is apt to acquire a distorted view of its value. It should be understood that the meaning of the Wasser-

mann test depends quite largely upon the technic and care used by the laboratory where it is performed. A certain number of active cases of syphilis in the third or tertiary stage will give negative Wassermanns. This is especially true if the cases have had partial antisyphilitic treatment and have relapsed because the treatment was not completed. It has been pointed out that syphilis may be the cause of miscarriage, stillbirth or of early death from congenital debility, or premature birth. These conditions are so frequently due to syphilis that it is believed advisable to examine the parents for syphilis and test their blood by the Wassermann method in all such cases. It is so important to protect the unborn child from syphilis that if one accepts at its face value the statement that 10 per cent of married women are syphilitic it might be worth while to consider the feasibility of a routine Wassermann test for all pregnant women. Certainly wherever such a woman has a history of previous miscarriage or there is other reason for suspecting syphilis, both a clinical examination and a Wassermann test should be made. In all cases where syphilis is discovered in a pregnant woman, vigorous treatment should be given. The best way to treat a syphilitic child is to treat the mother before the child is born. As a general measure of protection for future children, all cases of venereal sore should be given very careful attention. It is now possible by means of the "dark-field" method of examination to find the germs of syphilis even in the first sore of the disease. If treatment is begun in a very early stage of the disease, a speedier cure may be expected than if treatment is begun later. When treatment is not begun until the rash appears on the body, the courses of treatment with alternating periods of rest must be kept up for a period of two or three years in order to insure against relapse.

**Notes on the Preservation of Stock Strains of *Treponema Pallidum* and on the Demonstration of Infection in Rabbits.**—Wade H. Brown and Louise Pearce, New York. *Journal of Experimental Medicine*, 1921, vol. xxxiv, p. 185.

Experiments carried out on rabbits infected with *Treponema pallidum* showed that there was a constant invasion and localization of the organisms in the superficial lymph nodes, that the infection persisted indefinitely, and that organisms could be recovered at any time from such nodes as the popliteals. Based upon these observations, a method is proposed for the preservation or recovery of stock strains of *Treponema pallidum* and for the demonstration of infection in rabbits.

**Syphilis in Women and Children.**—Walter C. Swayne, Bristol, *British Medical Journal*, 1921, No. 3169, p. 476.

There are greater difficulties in women than in men, owing to the frequent failure of the patient to detect symptoms in herself. A very large number of those affected contract the disease innocently. Women are, on the whole, more likely to act as innocent carriers than men, especially of extragenital

infections. Diagnosis is, on the whole, more difficult with women than with men. Treatment is often interfered with by home duties, conditions of employment, pregnancy, and parturition. The special social and family surroundings of women make the disease in their case more difficult to deal with, and perhaps of more importance than in the male. Quite a large proportion of women suffering from syphilis come, sooner or later into the hands of the gynecologist for the treatment of various pelvic affections.

**A Memorandum of the Occupational Study of Syphilis, With Special Reference to Farmers.**—John H. Stokes and Helen E. Brehmer, Rochester, Minn. *American Journal of the Medical Sciences*, 1921, vol. clxii, p. 572.

A survey of syphilis in 100 farmers whose records were taken at random from the files of the section of dermatology and syphilology in the Clinic reveals no distinctive difference between the clinical picture of the disease in farmers and that in railroad men. This result is not to be interpreted as precluding the possibility of special occupational types in the disease. For the determination of such types the investigation must be taken to the groups instead of subjecting the group to a species of unconscious medical selection involved in resort to a diagnostic clinic. The figures given in the table therefore present essentially the diagnostic problem of late syphilis in general medicine. They suggest further that physicians at large could profitably give less attention to the history of infection and the serum Wassermann test and more attention to the spinal fluid test and to the physical and especially the neurologic and ophthalmic findings in their effort to recognize late syphilis and to interpret the medical picture presented by a given patient.

**A Comparative Study of Syphilis in Whites and in Negroes.**—Ernest L. Zimmermann, Baltimore. *Archives of Dermatology and Syphilology*, 1921, vol. iv, p. 75.

Extragenital infection is relatively infrequent in negroes. Among colored males and females the age of infection is respectively one and two years earlier than in white males and females. Secondary syphilis in the negro is characterized by marked polyadenitis, by frequent and severe osteoarthritic symptoms, by the frequency of iritis, and by the high incidence of follicular and pustular syphilids. A striking racial peculiarity is the frequent occurrence of the annular papular syphiloderm. Bone syphilis is the most frequent lesion of tertiary syphilis in the negro, exceeding neurosyphilis, which in white patients comprised almost half of all late manifestations. Cardiovascular syphilis is more frequent in the negro, with an incidence of two to one in colored and white males, respectively. Stricture of the rectum and elephantiasis vulvae are extremely common in the colored female. Leukoplakia is rare in the negro. Tertiary adenitis is common in the negro. Neurosyphilis is more frequent in white patients than in negroes. The negro is less likely to develop tabes or paresis, while the large group of unclassified cases of cerebrospinal syphilis is approximately of equal frequency in the two races.

In negroes it is especially likely to manifest itself in the form of cerebral endarteritis. In respect to syphilitic infection there exist inherited biologic differences between white and negro patients. The negro develops intense reactions on the part of cutaneous and osseous structures, and is relatively free from tabes and paresis. In white patients, syphilis more frequently runs its course with skin manifestations slight or absent, but there is a greater tendency toward the eventual development of tabes or paresis.

**Experimental Syphilis in the Rabbit. VII. Affections of the Eyes.**—Wade H. Brown and Louise Pearce. New York. *Journal of Experimental Medicine*, 1921, vol. xxxiv, p. 167.

From the study of a number of instances of eye infection in the rabbit, it was found that a variety of affections might occur following scrotal or testicular inoculations of *Treponema pallidum*. Those observed included ciliary injection, conjunctivitis, keratitis and iritis which might occur separately or in combination with one another, except that keratitis and iritis were always accompanied by a reaction in the ciliary vessels and usually by a conjunctivitis. Several forms of each of these affections were described, and while some of them were regarded as presenting a very characteristic picture, it was recognized that the conditions present in other cases were not sufficiently distinctive to permit of a clinical diagnosis. With a few exceptions, however, the pathology of the lesions was sufficient to identify them as processes of a syphilitic nature. It was also found that this group of lesions usually arose from a common focus of infection which was located in the episcleral tissues immediately surrounding the cornea. From this point, the infection tended to spread to the conjunctiva and the cornea, or toward the canal of Schlemm and the spaces of Fontana and thence to the ciliary body, the iris, and the choroid. The localization of the lesion and the mode of extension were held to be responsible for the combination of manifestations usually observed. From an analysis of the circumstances under which affections of the eyes occurred it was found that the great majority of them occupied a definite position in the scheme of tissue reactions, being the only generalized lesions developed or the last type of lesion to appear. These facts, together with the unusual frequency of relapse in these affections, were believed to indicate that a low degree of protection was conferred upon these tissues by reactions taking place elsewhere and that the protection afforded by the local reaction was of a feeble character. This deduction was in part confirmed by the fact that it was found to be possible to increase or decrease the incidence of eye lesions by the use of experimental means which varied the scheme of reaction in animals inoculated with a given strain of *Treponema pallidum*.

**Immunity Studies in Experimental Syphilis.**—Frederick Eberson, St. Louis. *Archives of Dermatology and Syphilology*, 1921, vol. iv, p. 490.

The blood serum from persons having latent syphilis was found to have spirocheticidal properties. Rabbits were protected uniformly against infec-

tion with virulent *Spirocheta pallida* in combination with such serums. Protective properties were found in the serums of asymptomatic persons with latent syphilis with the following histories. Infection with syphilis dating back from three to twenty-five years. Patients who had received treatment until the Wassermann reaction had become negative. A number of patients who had no history of infection, who had taken no treatment, and who had a slightly positive Wassermann reaction usually in the cholesterin antigen. A group of patients in whom the Wassermann reaction was slightly positive in the cholesterin and noncholesterin antigens, or strongly positive in either one, in inverse relationship. An infant whose mother's serum was found to contain spirocheticidal properties. Spirocheticidal activity of serums in latent syphilis is of such a character as to prevent the normal dissemination of *Spirocheta pallida* from a primary focus. Failure to inoculate rabbits with mixtures of serums and spirochetes was correlated with negative inoculations with the blood from such animals. In the experimental animal, spirochetolytic serum may be developed in the course of six months to one year after the infection. In the rabbit, as in man, protective substances are found at a time when the infection has attained a relatively latent state. The presence of these substances in given serums apparently depends on the stage of infection. When definite latency has been established, the serum appears to protect against experimental inoculation, whereas the serum from cases of early syphilis or those in which true latency has not been attained is not spirocheticidal. Spirocheticidal activity is essentially a function of time and depends on the degree to which the individual has elaborated and distributed the slowly accumulating antibodies. Serums which were developed in rabbits by strains of *Spirocheta pallida* from latent sources manifested a wider range of protective properties, as shown by the inhibitory effect on heterologous as well as homologous strains. Serums from latent cases behaved similarly. Chancre strains when used for experimental infection were not capable of developing spirocheticidal serums for heterologous organisms, in the few experiments which were attempted. A negative Wassermann reaction following anti-syphilitic treatment may or may not go hand in hand with spirocheticidal activity of serums. Continued treatment which renders a Wassermann reaction negative does not appear to nullify any existing protective property of the given serum. By analogy with trypanosome and spirillary diseases and the carrier state of certain well-known infections, syphilis offers immunity phenomena which tend to explain latency on the basis of a blood immunity which is developed progressively from tissue immunity. The mechanism by which immunity in syphilis develops would seem to be an elaboration of antibodies commencing at the time when initial lesions are present and continuing as a progressive extension of local immunity from one group of tissues to another until the immune substances are absorbed by the blood stream. Latent *Spirocheta pallida* thus become innocuous for the host. The presence of *Spirocheta pallida* at certain times in the human or animal body need not imply disease but rather a latent stage in which the spirochetes are able to survive in the immunized body. Failure to reinfect with syphilis means, from this



point of view, the entry of spirochetes into surroundings which favor lodgement without setting up of visible lesions or manifestations. Immunity need not imply a condition which is incompatible with the life of a parasite. Latency, then, connotes a balance that has been struck in the individual between the antibodies and the invading parasites. The results of the experiments reported in this paper suggest that the serum from definitely established latent cases of syphilis may prove of therapeutic value.

**The Genesis of Neurosyphilis.**—Joseph Earle Moore, Baltimore. *Archives of Dermatology and Syphilology*, 1921, vol. iv, p. 55.

In fifty-four cases of syphilis in all stages of the disease, but without demonstrable neurologic involvement, an early negative spinal puncture was repeated, with positive results in two. In one of the positive cases, invasion of the central nervous system had apparently taken place by direct extension from a gummatous periostitis of the inner cranial table; in the other, it probably occurred during a second period of generalization of the disease. In the majority of cases of neurosyphilis, invasion of the central nervous system takes place during the first few months of the infection; but in some cases it may occur at any time during the course of syphilis by one of the two mechanisms outlined. The appearance of recurrent secondary syphilis or the recurrence of a positive blood Wassermann reaction after a lapse in treatment is the probable outward manifestation of a fresh generalization of the disease, and should be made the occasion for reexamination of the cerebrospinal fluid.

**The Pathology of Syphilis of the Central Nervous System With a Digest of Serological Reactions.**—Robert A. Keilty, Danville, Pa. *New York Medical Journal*, 1921, vol. cxiv, p. 497.

Syphilis of the central nervous system can be controlled and by intelligent handling can be almost eliminated. This is possible only by a complete understanding of prophylaxis and by an adequate and faithful treatment in the early stages. Syphilis of the central nervous system in the later stages, both neurologically and psychologically, is an incurable disease because of the very nature of the pathologic changes. Syphilis is distinctly a productive disease building up the fixed tissue types of cells, increasing the fibrotic changes, increasing the character of the arteriocapillary walls, decreasing their permeability and interfering with the interchange between the chemical value of the blood and the metabolism of the parenchymatous cells. Syphilis by reason of its productive changes produces generative metamorphoses in smaller or larger groups of parenchymatous cells, which in the case of the central nervous system results in irreparable damage. Syphilis produces specific reactions in the nature of gummata which are not as important as its more diffuse changes but which are destructive in nature and therefore from the symptomatologic viewpoint are in relation to tumor formation. Serologic reactions are to be taken as great aids but are not to be considered the sole reliance upon which a diagnosis may be based.

**The Syphilitic Factor in Essential Epilepsy.**—N. Novick, East Norfolk, Mass. Public Health Reports, 1921, vol. xxxvi, p. 2058.

In the light of the present usage of the plural term "epilepsies", intended to comprise a group of disease conditions in which the nature of the seizure manifestations varies and in which the etiology of the convulsive attacks possibly differs, the writer endeavored to determine the incidence of syphilis in a series of established institutional cases of essential epilepsy as evidenced by history of primary infection, clinical manifestations, and corroborative evidence of the Wassermann reaction. In 231 cases the incidence of syphilis was found to be 2.2 per cent. These cases are viewed in the light of the probability of the luetic infection existing side by side with the epilepsy; the seizure manifestations may or may not be traced to the specific involvement, but are perhaps aggravated by the latter disease. The occurrence of a syphilitic factor in epilepsy as evidenced by repeated positive Wassermann tests alone, in the absence of clinical support, as far as it was possible of determination, was found in 2 per cent of the cases. This small percentage might, perhaps, constitute the possible syphilitic etiology of epilepsy as determined in a series of 245 cases. Further proof cannot be offered.

**A Possible Explanation of the Increased Incidence and Early Onset of Neurosyphilis.**—A. Reith Fraser and A. G. B. Duncan, British Journal of Dermatology and Syphilis, 1921, vol. xxxiii, p. 281.

The responsibilities for the increasing incidence of early neurosyphilis rest with: (a) The tendency to treat primary syphilites *en masse*. (b) The method of working to a mechanical time-table. (c) The blindfold method of working for a serological rather than a clinical cure. (d) Failure to interpret pathologic findings in the light of the clinical picture. (e) Losing sight of the importance of the central nervous system as regards the patient's future. (f) The tendency to undertreat patients. Modern early treatment fails in protecting the nervous system by rapidly sterilizing the general systemic system, and thus depriving the cerebrospinal axis of its antibody supply. In addition, the large doses of arsenobenzine employed tend to damage the central nervous system. The possible damage to the cerebrospinal axis resulting from the strain and anxiety of war must be kept in mind as a predisposing factor. The nervous system is invaded coincident with the generalization of the organism. Nervous system involvement may be symptomatic or asymptomatic. In the absence of clinical signs a normal spinal fluid may indicate the successful overcoming of the organism by the nervous system or the failure of the nervous system to react. It may also suggest that the general systemic circulation has been successfully sterilized before the cerebrospinal axis was invaded. A pathologic spinal fluid may indicate damage or protective reaction. In the absence of symptoms we cannot accurately interpret the finding. For the security of the patient the early invasion of the cerebrospinal axis should be taken for granted. The occurrence of neurosyphilis is influenced by (a) the patient's power of

resistance, (b) the natural resistance of the central nervous system and its inherent capacity for producing antibody, (c) the stage at which treatment is inaugurated, (d) the type of treatment employed, (e) the period over which treatment is carried out, and (f) the type of parasite responsible for the infection. In this connection the question of a life-cycle of the *Spirocheta pallidum* must be considered. Great importance is attached to the value of clinical acumen, observation and judgment. These should be correlated with careful interpretation of pathologic findings. The importance of treating each particular case on its merits instead of treating him as one of a series is emphasized. Treatment should aim at conserving sufficient antibody for the requirements and protection of the cerebrospinal axis, instead of defeating one's object by rapid sterilization of the general systemic system, thereby leaving the nervous system to look after itself—a thing for which it is ill-equipped. Antibody supply should be conserved over a period of years. The value of intramine as a protection for the nervous tissues warrants its inclusion in any scheme of treatment.

**Syphilis and Tuberculosis.**—Lester Hollander and Frederick C. Narr, Pittsburgh. *Archives of Dermatology and Syphilology*, 1921, vol. iv, p. 153.

A case has been presented in which the patient showed gross syphilitic and tuberculous lesions. Available statistics of the coexistence of syphilis and tuberculosis have been reviewed. The possible malignancy of tuberculosis in the case described is attributed in part at least to iodide medication.

**The Influence of Syphilis Upon the Pregnant Woman.**—George Gellhorn, St. Louis. *Surgery, Gynecology and Obstetrics*, 1921, vol. xxxii, p. 535.

Discussions on syphilis in pregnancy have, in the past, been limited almost altogether to the harm that may befall the unborn child; and most of the textbooks on obstetrics convey the impression that the mother has nothing to fear from the disease. While this is true of a very large percentage of the cases, the writer has attempted to show from personal observations and a review of the available literature that syphilis is capable of producing real complications—whether in pregnancy by impairing the general health of the patient, or in labor by obstructing the birth passages or causing other more or less serious damage, or else in the puerperium by adding to the morbidity and mortality of that state. And who is there to tell just when any of these complications may arise in a given case, or to what extent they may endanger the patient's life? The very uncommon personal observation recorded by the writer above, sounds an additional note of warning. The practical conclusion is very obvious. Knowing that both mother and child are endangered, we must ever bear in mind the possibility of syphilis, particularly when we have to deal with obscure recalcitrant disturbances in pregnancy, and once our diagnosis is made, we must give energetic and systematic treatment to such women throughout the period of pregnancy.

**Chronic Fibroid Subcutaneous Syphilomata.**—Herman Goodman, New York. *British Journal of Dermatology and Syphilis*, 1921, vol. xxxiii, p. 335.

The author has presented the case-history and findings of a patient who presented subcutaneous syphilitic nodules for a long period of years, and which clinically did not show any evidence of ulceration. He has reviewed a second case in which syphilitic nonulcerating nodules had been present subcutaneously for many years apparently attached to tendon. He has also referred to the report of Weber of a similar case. Histologically the characters of the lesions were essentially those of chronic granulomata. Antisyphilitic treatment in the case here reported for the first time cleared the lesions. Lesions such as are here described have not been widely discussed, and it is hoped that further observations will be published to clear this baffling question.

**Syphilis of the Lung.**—Rolla G. Karshner, Los Angeles, and Clyde F. Karshner, Chicago. *Annals of Medicine*, 1920, vol. i, p. 371.

One hundred and twenty cases of syphilis of the lung have been carefully selected from the literature and analyzed. The history of syphilis of the lung is as old as the history of syphilis. Syphilis of the lung occurs more frequently than it is recognized. The disease has been most commonly recognized in the early part of the fourth decade of life. It is more common in males than in females, and more fatal in the latter. As recognized in the past, lung accidents are among the latest manifestations of the disease. Ten per cent of the cases occurred as late involvement in hereditary syphilis. Fifty-five of the 120 patients came to autopsy. Out of 66 patients treated, 56 were cured, 5 improved, 1 showed no improvement and 4 died. Eighty per cent of the cases showed concurrent or previously active syphilitic lesions which were clinically recognizable. In addition to this all of the hereditary cases were stigmatized. Syphilis of the lung is relatively common in association with bone, cutaneous and visceral syphilids, rare in association with central nervous involvement. Twenty per cent of the cases with autopsy showed amyloid changes in other organs. Twenty per cent had syphilitic aorta and forty per cent syphilitic livers. Trauma apparently plays a very small part in the localization of the spirochete in the lung. None of the cases had previously received proper antisyphilitic treatment; in most, treatment had been desultory. In 37 per cent of the acquired cases primary infection was denied. Of the 55 cases with autopsy only 4 were correctly diagnosed antemortem. Fifty-five per cent of the cases had been diagnosed and treated as pulmonary tuberculosis. In 24 per cent the diagnosis was made upon the appearance of associated syphilitic lesions. In 35 per cent of the cases the diagnosis was determined after the therapeutic test. Syphilis of the lung in the early secondary or florid period of infection is not well established. However, it is reasonable to believe that lesions corresponding to the cutaneous exanthemata may well occur in the lung at the time of the generalized spirochetosis. Syphilis of

the lung occurring together with pulmonary tuberculosis is the commonest type of syphilitic pneumopathy. The pathology of syphilis of the lung is the new pathology of syphilis established by Warthin, and the diagnosis is essentially microscopic. Syphilis of the lung is commonly classified as, (a) interstitial pneumonia, which occurred in 50 per cent of the cases with autopsy, (b) gummata, which occurred in 59 per cent of the cases with autopsy, (c) syphilitic pulmonary sclerosis or fibrosis, which occurred in more than 50 per cent of the cases with autopsy (d) bronchiectasis, which occurred in 47 per cent of the cases with autopsy, and (e) suppurative processes, ulceration and gangrene. Suppuration was noted in 13 per cent of the cases with autopsy, cavity in 22 per cent of the cases with autopsy and gangrene in 1 case with autopsy. The symptoms of pulmonary syphilis are the symptoms of pulmonary tuberculosis. The physical signs of pulmonary syphilis resemble the physical signs in pulmonary tuberculosis. In the clinical cases without autopsy the upper lobes were involved about twice as commonly as the bases. Nearly half of the cases showed involvement of both lungs. The roentgen ray has been a valuable factor in the past in differentiating syphilis of the lung from other conditions. It should become increasingly valuable in the future. At autopsy both lungs were involved in 36 per cent of the cases. The lesions were much more common on the right side, 63 per cent showing involvement of the right lower lobe, 55 per cent of the right upper lobe, and 43 per cent of the right middle lobe, while only 36 per cent showed involvement of the left upper lobe and 36 per cent of the left lower lobe. Syphilis of the lung most frequently involves the upper lobes first, the process proceeding downwards. It is more common on the right side. Pathology in the apices by no means precludes the possibility of syphilis. Involvement of the middle or bases of the lungs speaks for syphilis.

**Visceral Syphilis.**—Udo J. Wile and Clement H. Marshall, Ann Arbor, Mich. Archives of Dermatology and Syphilology, 921, vol. iv, p. 37.

Acquired pulmonary syphilis is exceedingly rare pathologically, and it is even more rare as a clinical picture. In congenital syphilis it is a not infrequent pathologic picture in the form of the well known white pneumonia. As a diffuse sclerosis and as small gummas, it is also encountered clinically, and subsequently it is encountered as a pathologic picture in the congenital form of the disease. Difficult as is the gross pathologic picture, the clinical picture of pulmonary syphilis is even more difficult of recognition. In the last analysis, it must be admitted that with the present standards, no case of clinical pulmonary syphilis can be absolutely accepted without a pathologic examination. It is now a well accepted fact that syphilis and tuberculosis may, and frequently do, occur together. It has been a frequent observation that latent tuberculosis is very apt to become activated in the presence of active syphilis. Conversely, it may be accepted that a pure syphilitic process in the lung, existing unrecognized, constitutes an admirable site for the implantation of the tubercle bacillus. While the proof of clinical pulmonary syphilis must be sought and

found at the postmortem table, there is, nevertheless, a small group of cases in which the evidence is even more than presumptive that one is dealing with pure syphilis of the lung. These are cases in which, for the most part, the processes are atypical, both clinically and in their course. There are cases in which the pulmonary symptoms may be either coincident with early syphilis or present with manifest constitutional syphilis of other viscera, in which prompt amelioration or even complete disappearance of signs and symptoms results on the institution of antisyphilitic treatment. Such cases as these, if carefully worked up, in which tuberculosis has been eliminated in all probability, and in which the last proof is lacking by reason of the patient's survival, must be accepted as presumptive examples of syphilitic pulmonary disease. During the last two decades reports of about fifty such cases have been found in the literature. For the most part they have been carefully studied by competent observers, and we feel that they may justifiably be taken as various examples of syphilitic disease, as far as clinical medicine can go in the diagnosis of this condition. From a study of these cases, and of a few which belong in this group which the authors have been able to study in the university hospital, it appears that clinical pulmonary syphilis in the acquired form of the disease may occur: (1) as isolated gummas of the lung; (2) as diffuse syphilitic fibrosis, and (3) possibly as a diffuse bronchopneumonia. Of the above mentioned three forms, chronic fibroid changes in the lung are described as the most frequent. Undoubtedly, some of these are the result of the breaking down and slow absorption of larger and smaller gummas, and it is not unlikely that, as in syphilis of the liver, one is dealing not so much with a variety of form as with a difference in the time at which the patients are studied. Thus, for example, it may be accepted that the interstitial fibroid condition, the so-called syphilitic phthisis, is a late result, being, in fact, an analogous picture to the interstitial hepatitis found as a terminal picture either of isolated or of diffuse syphilomas in the liver. The picture of "syphilitic bronchopneumonia" constitutes a disputed field. That symptoms of an acute or subacute pneumonia with diffuse patches of consolidation, either more or less severe, are occasionally met in the course of pulmonary syphilitic disease is accepted. The explanation that these symptoms are themselves due to syphilis, however, is disputed. Gumma of the lung, recognizable as such clinically and pathologically, is said to be exceedingly rare. The authors believe, however, that it is not so infrequent as the initial stage of a fibrosis and of later cavitation. When found, the gumma is somewhat more frequently described as occurring in the right lung, usually in the middle or lower lobe, and frequently near the hilum. Chronic interstitial pneumonitis due to syphilis is the most common form of accepted syphilitic pulmonopathy. Pathologically, this is the expression and end-result of all other syphilitic processes. This stage, as it may properly be called, of syphilitic lung disease is that most frequently studied clinically. It is in this form that symptoms are most frequently encountered, due either to a loss of lesser or greater portions of pulmonary tissue, or to their loss of function. The chief characteristics of the condition pathologically are a radiating fibrosis

extending out from the hilum through the bronchi and of the bands extending from the pleura into the substance of the lung. Associated with this are isolated fibroid masses throughout the substance of the lung representing areas of more diffuse syphilomatous tissue. In a general way the prognosis of pulmonary syphilis may be said to vary directly with the time at which a correct diagnosis is established. In the early cases, in gummas and in the earlier stages of the chronic fibroid type, the prompt institution of antisyphilitic treatment undoubtedly offers a fair prognosis in the condition. If extensive fibrosis and destruction have taken place, a condition analogous to that seen in chronic interstitial hepatitis is found. A marked general betterment in the patient's condition may be expected as a result of the institution of treatment directed to the disease as a whole, but little change can be expected in the signs or symptoms of the pulmonary condition. The prognosis is materially influenced, however, by the association of tuberculosis. The presence of both conditions adds a more serious prognosis than either one or the other case alone.

**Visceral Syphilis, Especially of the Central Nervous System and Cardiovascular System.**—T. Clifford Allbutt, Cambridge. *British Medical Journal*, 1921, No. 3162, p. 177.

The syphilitic process may be seen little in the primary sore. Wherever it be found it consists in a lympharteritis with consequential irritative and atrophic effects. The division of syphilis into time periods—as primary, secondary, tertiary, and visceral—is based upon superficial characters, and is misleading. The pyrexial phase, slight, as it may be, indicates a general syphilitic sepsis, in which the cerebrospinal system is soon involved. Early necropsies have shown that in the pyrexial phase the aorta, brain, liver, and other viscera become infected; and that the cerebrospinal system does not long escape. Lumbar puncture should be made soon after the onset of the pyrexial phase, and the cerebrospinal fluid tested from time to time parallel with the blood testing.

**Studies in Asymptomatic Neurosyphilis.**—Albert Keidel and Joseph Earle Moore, Baltimore. *Archives of Neurology and Psychiatry*, 1921, vol. vi, p. 286.

Group 1.—Normal fluids. Neurosyphilis is not definitely ruled out, but we have no means of predicting which cases will later show abnormalities, except by animal inoculation experiments. The great majority of patients in this group certainly remain free from late clinical or serologic evidence of neurosyphilis. Group 2.—Neurologic damage minimal or questionable. The spinal fluid shows pleocytosis and increased globulin content, but negative Wassermann and colloidal gold and mastic tests. These findings may be in some cases the expression of meningeal irritation only, without definite tissue invasion. Patients showing this type of spinal fluid uniformly do well on routine treatment without the

addition of intraspinal therapy. The routine may be that for patients without spinal fluid changes. Group 3.—Tissue invasion moderate. The usual early complaint is headache. The spinal fluid shows cells from 10 to 100, usually less than 50; globulin one-plus or two-plus; the Wassermann reaction is negative with small quantities of fluid, and either positive or negative with larger amounts; colloidal gold curve syphilitic or meningitic zone; mastic curve to 3, or, in some instances, paretic. In general this type of patient does well, both clinically and serologically, on routine treatment without intraspinal therapy. However, the authors believe that to obtain the best results the dosage of arsphenamine and the number of doses to a course should be increased over the routine used for patients without neurologic invasion, that the interval between doses should be decreased, and that the total amount of arsphenamine administered should be relatively greater and the total amount of mercury relatively less than in uncomplicated cases. In only one instance have they found it necessary to resort to intraspinal therapy in order to accomplish a serologic cure. It is probable that spinal fluid changes of this type represent future meningovascular cerebrospinal syphilis, though a minority of the patients may ultimately develop parenchymatous neurosyphilis. Group 4.—Tissue invasion definite. Complaint may be absent, or may be that of nervousness, lassitude or neuralgic pains. If careful sensory examination is omitted, neurologic abnormalities are not detected. The spinal fluid shows from 10 to 100 cells, usually more than 50; the globulin is greater in content than in the preceding two groups, ranging from three-plus to four-plus; the Wassermann reaction is positive with 0.2 c.c., or less, and the colloidal gold and mastic curves are paretic. The majority of patients in this group are not serologically cured by routine treatment, regardless of alterations in the individual dose or the total amount of arsphenamine or the interval between doses. An occasional patient may be serologically improved, but the improvement is difficult or impossible to maintain. If, after six months' treatment, no change in the intensity of the spinal fluid findings is manifest, intraspinal treatment is an indispensable adjunct to routine treatment. Even when this plan is adopted, improvement, which may be looked for in a large percentage of the cases, is slow and treatment prolonged. In all probability, this group represents future cases of parenchymatous neurosyphilis—paresis and tabes. Indeed, the authors have observed the development of paresis in two patients with such spinal fluid findings discovered early in the course of syphilis.

**The Early Manifestations of Syphilis of the Central Nervous System.**—E. M. Hammes, St. Paul, Minn., *Journal-Lancet*, 1921, vol. xli, p. 483.

A routine examination of the spinal fluid should be made in every case of syphilis. Treatment should be continued until the patient is not only free from clinical manifestations, but until his blood and spinal fluid have become normal. With our present laboratory methods and clinical knowledge, syphilis of the nervous system can be diagnosed in its incipency, and, if properly and persistently treated, the grave degenerative forms can be reduced to the minimum.



**Diagnosis of Syphilis.**—Godeau (Antwerp). *Archives médicales Belges*, June, 1921, lxxiv, 6.

The known extreme frequency of syphilis in all countries should facilitate the diagnosis; nevertheless the disease is constantly overlooked. This is of course due to the coexistence of other maladies, the masking of other maladies by syphilis, the innocent character of some cases in which the patient is wholly unaware of his exposure and infection, the high moral character and innocence of some victims, the extreme vagaries of the inherited types, etc. There must also be added the constant deception practiced by many victims who admit nothing and deny everything.

The author does not at once proceed to the laboratory resources but enumerates the common sequence of symptoms, the traces of the chancre, the presence of stigmata in hereditary cases and the other clinical finds including the treatment test. Today this kind of evidence can be used only in the absence of laboratory facilities. The blood Wassermann is open to but few criticisms. If a subject with chronic nephritis give a strongly positive reaction this does not exclude the possibility that the local lesion is due to some other causation; this is of course obviously true of many other local alterations. Then, of course, a single negative Wassermann means nothing either way. When despite the negative seroreaction, we feel that the subject may have syphilis or that he is not yet cured, one makes use of a provocative test—the Herxheimer reaction. The trial treatment advised by the author, when it involves the intensive use of salvarsan, is not sanctioned by some syphilographers.

**Unrecognized Syphilis.**—Malcolm Seymour, Boston. *Boston Medical and Surgical Journal*, 1921, vol. cxxxv, p. 288.

Syphilis is a very prevalent disease. In the consideration of almost any disease, a physician should not hesitate to make a tentative diagnosis of syphilis. The signs and symptoms may only remotely suggest syphilis, but careful inquiry as to past history, together with painstaking physical examination of the patient and perhaps of others of the family, may reveal bits of evidence which taken singly may be of no importance, but when taken as a whole may make the diagnosis of syphilis unquestionable. Any patient, forty-five years of age or over, who shows an increase in blood pressure should have the benefit of a Wassermann test. Should this be negative, it is only fair to the patient to apply the therapeutic test, using potassium iodide, mercury, salvarsan, or all of these in combination for a period long enough to prove the possibility of syphilis.

**Staining of Spirocheta Pallida by the Fontana-Tribondeau Method.**—Cesar Fuentes, Havana, Cuba. *Archives of Dermatology and Syphilology*, 1921, vol. iv, p. 448.

Burnt alcohol fixation is not necessary, but is, on the contrary, rather harmful to the morphology of *Spirocheta pallida*. Ruge's solution is sufficient for fixation and dehemoglobinization. This solution can, however, be substituted

by  $H_2O_2$ , one-third in water and 1 c.c. formaldehyde, making a volume of 100 c.c. Heat is not essential in order that the tannin may act as a mordant. Fontana's solution may act without heating. The best way to use the method consists in heating tannin until it steams, and applying silver nitrate for one or two minutes. The most typical forms of spirochete are seen when the method is applied cold.

**A Note Upon the Iodine-Phosphoric Acid Reaction in the Urine in Syphilis.—**

Robert A. Kilduffe, Pittsburgh, Pa. Medical Record, 1921, vol. c, p. 329.

The urine reaction described is unreliable and valueless as a means of diagnosis in syphilis.

**Studies on Complement Fixation.—**R. L. Kahn, Lansing, Mich. Journal of Experimental Medicine, 1921, vol. xxxiv, p. 217.

It is shown by complement fixation studies with protein antigens and specific immune rabbit sera that the rate of fixation of complement is determined by the concentration of antibodies in the immune sera, that the greater part of fixation of complement takes place during the first hour, and that fixation is practically completed at the end of 4 hours at ice box temperature. It is further shown that the rate of fixation of complement is practically the same at ice box, room, and water-bath temperatures, the tendency being for slightly stronger fixation at ice box temperature.

**The Sachs-Georgi Test for Syphilis.—**Frederic Parker, Jr. and Angelica V. R. Haigh, New York. Archives of Dermatology and Syphilology, 1921, vol. iv, p. 67.

The Sachs-Georgi reaction agreed with the Wassermann reaction in 93.07 per cent of 520 parallel cases. As performed by the method described, the Sachs-Georgi test gives no unspecific positive reactions as controlled by the Wassermann test, and also does not give as many positive reactions, especially in cases in which the Wassermann reaction is weak or doubtful. Because of its simplicity and apparent dependability, it deserves further study, especially in cases in which the clinical aspects can be definitely determined.

**Optimum Conditions of Fixation of Complement in the Wassermann Test.—**

R. L. Kahn, Lansing, Mich. Archives of Dermatology and Syphilology, 1921, vol. iv, p. 358.

The optimum conditions of fixation of complement in the Wassermann test with alcoholic extract and Noguchi antigens appear to be four hours at ordinary ice box temperature (from 6 to 12 C.) With cholesterinized antigens, a one-hour fixation period at ice box temperature is recommended. Ice box temperature renders the reaction somewhat sharper than water-bath temperature, and a one-hour period precludes the possibility of picking up false positive reactions with these antigens.

**The Present Status of the Luetin Reaction.**—Robert A. Kilduffe and Matthew E. Soller, Pittsburgh, Pa. *Archives of Diagnosis*, 1921, vol. xiii, p. 249.

The luetin reaction is without value and will give false and misleading results when iodide medication has been utilized within four weeks preceding or four weeks after the test. The test should, therefore, not be made when the patient is under medication. The luetin test has its greatest value in the tertiary and hereditary forms of syphilis in which the Wassermann test is also of great value. The luetin test cannot replace the Wassermann test in the diagnosis of syphilis. A negative luetin test is of greater value from a diagnostic standpoint than a positive reaction. A negative luetin test is of greater diagnostic value than a negative Wassermann test. The proper interpretation of the reaction requires a considerable degree of skill and experience. Definite statements as to the specificity of the reaction cannot be made until further and extensive investigations have been made. A negative reaction must be kept under observation, in doubtful cases, for at least three weeks in order to rule out a possible delayed positive. The luetin test, when properly performed, checked and controlled, can be looked upon as corroboratory and presumptive evidence of syphilis, but should always be checked by the Wassermann test.

**Comparison of Formol and Wassermann Reactions in Diagnosis of Syphilis.**—Enrique E. Ecker, Cleveland, Ohio. *Journal of Infectious Diseases*, 1921, vol. xxix, p. 359.

Of the total number of positive reactions obtained by the formol reaction of Gate and Papacostas, only 37.09 per cent agreed with the positive results obtained by the Wassermann method. A large number of formol positives (44 or 8.8 per cent of total) were of the plus type, and of these 13 (or 29.54 per cent) were positive by the Wassermann method. These weakly positive reactions tend to induce confusion, as it is often difficult to interpret these reactions. The reaction as it stands is of no diagnostic value because of its failure to react clinically and serologically clear cut cases of syphilis, and the occurrence of positive reaction in the absence of the disease.

**The Hecht-Gradwohl Test Employing Ice Chest Fixation.**—H. D. McIntyre, E. A. Worth and A. P. McIntyre, Cincinnati, Ohio. *Journal of Laboratory and Clinical Medicine*, 1921, vol. vi, p. 706.

Complement in human serum is sometimes an unstable thermolabile substance which will deteriorate even if subjected to a temperature of 37.5° C. for a period of one-half hour. In the Hecht-Gradwohl test this is what happens if the complement fixation takes place in the water-bath. The authors have encountered ten sera in which such deterioration of complement has occurred. This was determined by placing a serum in the water-bath for one-half hour titrating a portion of it at the same time and titrating a second portion which had been subjected to the water-bath temperature. Ten sera yielded a lower index on the second titration than on the first. This source of error is obviated if complement

fixation is carried out in the ice chest as the antigen containing tubes are then subjected to the water-bath temperature for only one-half hour. Furthermore, this test has all of the added advantages pointed out by Gradwohl in addition to the one just alluded to, as well as the advantage of ice chest methods of complement fixation which we have emphasized in an earlier paper. Theoretically the Hecht-Gradwohl test with ice chest complement fixation should be the test par excellence for the detection of antiluetic amboceptor in human serum. Practically, however, in a large series of cases, the ice chest Wassermann and the ice chest Hecht-Gradwohl tests would agree in nearly all instances.

**The Wassermann Test and Its Interpretation.**—R. L. Kahn, Lansing, Mich. *Journal of Laboratory and Clinical Medicine*, 1921, vol. vi, p. 579.

After all of the conditions outlined in the paper have been complied with, a positive Wassermann should be assumed to be evidence of the existence of syphilis. Needless to say that weak positive reactions should be fully correlated with the clinical signs before reaching a positive diagnosis. The blood of normal individuals will occasionally give a one-plus or plus-minus, particularly with a cholesterinized antigen. These weak reactions, in the absence of clinical symptoms or history, could undoubtedly be considered negative.

**The Sachs-Georgi Reaction in the Spinal Fluid of Patients With Syphilis.**—Ward W. Harryman, Ann Arbor, Mich. *Archives of Dermatology and Syphilology*, 1921, vol. iv, p. 299.

The results of the Sachs-Georgi reaction on the spinal fluid closely parallel those of the Wassermann test. The Sachs-Georgi reaction is a substitute or may be a valuable addition to the Wassermann test on the spinal fluid. The Sachs-Georgi reaction furnishes a means for an earlier serodiagnosis of central nervous system syphilis than the Wassermann test.

**The Laboratory Diagnosis of Syphilis.**—Walter E. King, St. Paul, Minn. *Minnesota Medicine*, 1921, vol. iv, p. 490.

Experimental syphilis in animals and the development of cultural methods are yielding results which are of fundamental importance in the study of the disease and its specific causative agent. These researches also may succeed in throwing light on some of the present obscure conditions pertaining to some of the specific infectious diseases of unknown etiology. The culture method may be used to advantage in the diagnosis of atypical initial lesions which do not disclose the *Spirocheta pallida* on dark-field examination. The results of recent experimental work show that the spirochete may spread, not only by continuity, but also by metastasis before the clinical diagnosis of initial syphilis is possible. This work needs corroboration before definite conclusions can be formed. The early diagnosis of the initial stage is of extreme importance from the point of view of treatment and permanent cure. The diagnosis should be confirmed microscopically. For routine work the suction apparatus, or cupping

tube provides a convenient means of securing clinical material. The use of the dark-ground illuminator (dark-field) is to be preferred to india ink smears or staining methods. There are several factors influencing the Wassermann test which should be known by every physician. Serum from an alcoholic patient may result negatively; presence of undue bacterial contamination in a specimen of serum will cause the appearance of a positive test; the peculiar wide variation in the complement-fixing power of the blood of certain patients may produce irregular results. Positive results may be obtained in cases of leprosy, hepatic disease, frambesia and scleroderma, or after the administration of an anesthetic. The literature covering the technic of the Wassermann test is full of suggested changes, many of which mark developmental stages in the theory and *modus operandi* of the reaction. Much study has centered around the standardization of reactions and proper antigens for use in conducting the test. It may be assumed that the employment of at least two antigens (cholesterinized and alcoholic extract) is important and essential for dependable results. A Wassermann test upon the cerebrospinal fluid, in certain instances, is of great diagnostic value. The reaction is positive in the tertiary stage, even when no clinical manifestations of the central nervous system are present. A positive test upon the cerebrospinal fluid of secondary or primary cases indicates involvement of the central nervous system. No case of syphilis should be discharged as cured until after a negative 1 c.c. cerebrospinal fluid test has been demonstrated. "The Provocative Wassermann" should not be disregarded by the physician but should be used in certain cases when considered necessary. The Wassermann has its "limits of delicacy." When confronted with Wassermann variations the physician should consider the biologic nature of the reaction. Carefully controlled reports show confirmatory results in the majority of tests performed by careful technicians. There is need, however, for the adoption of a standard method and perhaps State Board regulations and requirements for technicians. In the interpretation of the Wassermann test, the physician should bear in mind the following observations: In the initial stage of syphilis the weaker grades of reaction are of greater diagnostic value than in the late stages of the disease. The Wassermann test results positively in a relatively small percentage of cases up to the end of the second week after the appearance of the initial lesion. After the third week, fifty per cent or more of the cases will give positive reactions. A negative reaction is of the least value in the primary stage. In the secondary stage of syphilis, approximately 95 per cent of all cases result positively; therefore in the secondary stage dependence should not be placed upon the results of one negative test. In latent syphilis a weakly positive reaction should be regarded as significant. Lange's Colloidal Gold Test should be employed especially in cases of syphilis of the central nervous system. Physicians should make sure that the laboratory which carries out the test use extreme care in the preparation of the reagents used. With the colloidal gold test the paretic curve may be distinguished from the luetic curve. Globulin determination and cell count of the cerebrospinal fluid afford valuable confirmatory laboratory evidence in many cases.

**Standardization of The Wassermann Reaction.**—John A. Kolmer, Philadelphia. *Journal of the American Medical Association*, 1921, vol. lxxvii, p. 776.

The author feels quite sure that his new test will be simple for those who have had some experience in conducting complement-fixation tests. It will be difficult for the untrained; but this is probably true of all methods, and the attempts of the untrained to do the work are largely responsible for the unfavorable impression created by the Wassermann test in numerous localities and on numerous occasions. He bespeaks the cooperation of serologists and asks them to give the new test a fair and unbiased trial for the purpose of gradually adopting a technic which the majority of serologists can subscribe to as being worthy of adoption as a standardized fixation test for syphilis. At the present time he is engaged in extending the investigation into the field of complement fixation in bacterial and other protozoan infections and for the differentiation of proteins along the lines developed for complement fixation in syphilis.

**Comparative Results of Colloidal Mastic and Colloidal Gold Tests.**—Albert Keidel and Joseph Earle Moore, Baltimore. *Archives of Neurology and Psychiatry*, 1921, vol. vi, p. 163.

The results which the authors have obtained show that there is a fairly close parallelism between the colloidal gold and the colloidal mastic tests; and that when agreement is lacking, the mastic test seems to detect abnormalities more frequently than does the gold. This fact, and the simplicity of performance of the mastic test, lead us to conclude that the test should be an indispensable part of the routine of spinal fluid examinations.

**Preliminary Report on the Use of a Substitute for the Wassermann Reaction in the Serum Diagnosis of Syphilis.**—H. Marrian Perry and E. C. Lambkin, R.A.M.C. *Journal of the Royal Army Medical Corps*, 1921, vol. xxxvii, p. 161.

In this preliminary investigation, repeated quantitative estimations of the flocculating power of the serum in any particular case of syphilis have not been attempted, but the test has been applied solely to arrive at the comparability of the results obtained with those yielded by the Wassermann reaction. As has already been mentioned the cases examined were not chosen in any manner, and included treated and untreated patients in varied stages of the disease. Unfortunately, opportunity has at present been lacking of comparing the sensitivity of the heart extract we have employed with that used by the authors in their series of tests. The authors have, however, adopted the following arbitrary standard in the interpretation of the results of our examinations. Before including in their series any serum as positive, it must have, as a minimum, been capable of producing standard flocculation of the saline suspension of heart extract in a dilution of 1 in 2.5, i.e., in tube 2 of the first series. Applying this standard to the serums examined, the details of our findings are shown in a table. From this table it will be seen that in a series of ninety-four

cases of treated syphilis in which the Wassermann reaction had become negative, the Sigma test also yielded a negative result. In a series of eighty-three cases of treated and untreated syphilis, the result was positive by both tests. The observation of Dreyer and Ward that the highest unit-content of the serum is found in untreated cases in the secondary and tertiary stages of the disease was very clearly evidenced by the Sigma test, the untreated cases could be readily differentiated from the cases under treatment by the flocculation titre of their serums. In two cases of treated syphilis the Wassermann reaction was positive whilst the Sigma test gave negative results; in one of these cases the Wassermann reaction was returned by two independent observers as plus-minus, a degree of complement deviation which could not be considered as a positive result in the absence of a definite history of syphilis; in the second case a repetition of the Wassermann test the following day by an independent observer was positive. The examination of fifty normal healthy individuals without any evidence or history of syphilis was undertaken as a control. In every case the Sigma reaction was negative; in the lowest dilution (1 in 1.25) of these serums careful examination with a six-magnification lens failed to detect the slightest trace of flocculation. In two cases of this series the result of the Wassermann reaction was positive, but in both cases on repetition of the Wassermann test the result was returned as negative; this latter result was confirmed by an independent observer. In addition to the above cases 22 cerebrospinal fluids have been examined; 6 were positive and 14 negative by both reactions, whilst 2 were positive by the Sigma test and negative by the Wassermann reaction. These latter cases gave a definite history of syphilis and were considered as clinically typical of lesions of the central nervous system. The necessity for lowering the unit content in the case of cerebrospinal fluids was well demonstrated; the strength of the reaction in a positive fluid never approached that seen in the serum. The readings of the tests in all cases were definite and unequivocal, and no difficulty was experienced in classifying the grades of flocculation encountered in a positive serum. In order to avoid fallacies arising from bacterial contamination causing positive results, in cases where doubt existed as to the sterility of the serum, the presence of bacterial growth was excluded by cultural tests. The Wassermann test was in all cases undertaken by an expert in this examination; the method employed was that used at the Rochester Row Military Hospital as detailed in the Medical Research Council, Special Report Series No. 14.

**The Sachs-Georgi Precipitation Test For Syphilis.**—T. Taniguchi and N. Yoshinare, Glasgow. *British Medical Journal*, 1921, p. 239.

Heated serum should be used; unheated serums from positive cases may fail to cause precipitation in any concentrations (a wide range of concentrations has been tested). The concentrations of serum recommended should not be exceeded, since heated normal serums in large amounts—for example, 0.2 to 0.3 c. c.—may cause precipitation. No positive case has been met with in which the usual amounts of heated serum employed failed to show precipitate, but the reaction

may be more marked with 0.05 c.c. of serum than with 0.1 c.c. The mixture must be kept at 37° C., as precipitate may form with nonsyphilitic serums at lower temperatures. Sometimes, however, it is advantageous in the case of weak reactions to record the results after the tubes have stood for thirty minutes further at room temperature, but the behavior of the negative control must be carefully scrutinized. The results should be controlled by including in each series of tests known negative, weak and strong positive serums, just as in the case of the Wassermann reaction.

**The Clinical Interpretation of the Wassermann Test.**—A. R. Robertson, Seattle, Wash. *Northwest Medicine*, 1921, vol. xx, p. 215.

The author is convinced that the actual diagnosis of syphilis rests entirely with the clinician. He must regard the Wassermann test simply as a valuable instrument of precision, even as he regards his stethoscope. The stethoscope may fail to detect an early lung lesion because the signs are too faint. So, too, the Wassermann test may fail to detect very small amounts of antilipoidal substance. Each is an instrument, a very valuable instrument of precision, and the positive reaction of the Wassermann test is no less a trustworthy sign of disease than that which may be found by the stethoscope.

**A Good Wassermann.**—George Manghill Olson, Minneapolis. *Journal-Lancet*, 1921, vol. xli, p. 420.

There are many poor or incorrect Wassermans made at the present time. The fault and the responsibility for these incorrect Wassermann reports lie very largely with the laboratory. The only remedy the author can see for the cure of this condition is time. Gradually the technic in the laboratories will improve. The Wassermann reaction properly made is of fundamental importance in the diagnosis and treatment of syphilis. Unavoidable errors in the making of Wassermans should not exceed one-tenth to two-tenths of one per cent. At the present time we should use extreme care in making a diagnosis of syphilis on the presence of a positive Wassermann in the absence of other signs or a history of syphilis. It is possible to obtain two or more incorrect positive Wassermann reports on the same patient. Patients with no obvious signs or a history of syphilis, but in whom there is a report of a positive Wassermann, should be carefully examined for signs of syphilis, or referred to a syphilologist, before beginning treatment.

**Refractometric Studies With the Serums of Normal Rabbits Receiving Intravenous Injections of Arsphenamine and Neoarsphenamine.**—Keiichi Iokuda, Philadelphia. *Archives of Dermatology and Syphilology*, 1921, vol. iv, p. 616.

While it is impossible to draw any definite conclusions on the basis of so small a series of animals, the results are rather suggestive and warrant the publication of this preliminary note. When massive doses of either arsphenamine



or neoarsphenamine are administered intravenously at weekly intervals to normal female rabbits, there is a temporary decrease in the refractometric index of the serum owing to a diminution of the percentage of the various proteins. Irregular fluctuations in the curves follow with a final return to approximately their original values. When therapeutic doses of either of these drugs are given, there is a tendency toward decrease of the refractive index, with an increase in the relative amount of globulins. If the values are plotted at frequent intervals after a single therapeutic dose of either drug, we note a fall in the refractive index of the serum one-half hour after injection. The relative amounts of globulin show an initial fall with a tendency to rise during the first few days following the injection. In general, the changes induced by arsphenamine are somewhat more striking than when neoarsphenamine is employed, perhaps because of the greater volume of fluid injected in the former case. This problem requires further experimental study.

**Studies in the Serology of Syphilis. Syphilimetric Colorindices.**—Ernest F. Mahr, Washington, D. C. *Journal of Laboratory and Clinical Medicine*, 1921, vol. vii, p. 1.

The colorimetric scale makes it possible to determine with fair accuracy the finer gradations in the degree of syphilitic infection. Indices from one to four inclusive, for example, cannot be recorded other than "4-plus" by the regular Wassermann procedure. Doubtful readings, such as "plus-minus," 1-plus, and 2-plus are given a definite designation and are determined with greater certainty by the use of the color scale, and the personal equation of the observer is practically eliminated. In the case of subjects under antisyphilitic treatment, the recognition of a slight drop toward the negative side is possible with the use of the color scale, and practically impossible with the routine Wassermann. Slight increases to the positive side are recognizable in the same manner. With parietic spinal fluids it is seen that the syphilimetric index approaches the reading of "0" in proportion as the colloidal gold reaction shows a definite parietic curve, whereas the routine Wassermann reading will give simply a "4-plus" reading whether the curve is of a strong parietic type or not. The syphilitic zone of gold curve predominates in the region of indices from "6" to "8", and the parietic type in the region from "6" to "0." Colorimetric readings make possible the recording of the laboratory history of syphilis for each patient upon a graphic chart, giving a clear representation of the progress of cases under treatment. In Fig. 3 is suggested a method for the drawing of charts.

**The Ice-Box Modification of the Wassermann Test in the Diagnosis and Treatment of Syphilis.**—Albert Keidel and Joseph Earle Moore, Baltimore. *Bulletin of the Johns Hopkins Hospital*, 1921, vol. xxxii, p. 296.

In presenting this study the authors wish to express their realization of the danger attached to modifications of the Wassermann test which tend to increase its delicacy unwisely. The mechanism by which this is accomplished at low temperature incubation is not wholly understood. If it is due to deterioration

of complement in some manner dependent on factors not connected with changes in the patient's serum resulting from the disease process, its usefulness as a diagnostic procedure is vitiated. Modifications and technical fads have done much to discredit the Wassermann reaction. Incredible errors occur daily from such practices with the most distressing consequences. An erroneous diagnosis of syphilis based on a nonspecific positive Wassermann, even when subsequently corrected, leaves a trail often impossible to obliterate. A negative Wassermann resulting from technical error leaves the door open for a future diagnosis; but a false positive, particularly if followed by antisyphilitic treatment, shuts out this possibility indefinitely, if not forever. The study which they have presented is intended to demonstrate the results of the ice-box method in cases well studied and not dependent for diagnosis on this method. Although the series is small for such a purpose, it has demonstrated to their satisfaction an important superiority in its selection of uncured treated syphilitics. Although they favor its employment for diagnosis, as yet they do so guardedly, and accept no positive results without careful scrutiny of all available data in the case.

**The Accuracy of the Formalin and Sachs-Georgi Tests for Syphilis.**—W. Neave Kingsbury. *Lancet*, London, 1921, vol. cci, p. 799.

The results obtained from the formalin test prove once again the futility of basing conclusions on figures derived from a small number of cases, as small series have recently been published showing complete concord between formalin and Wassermann results. The technic of the test is simple, and were the results reliable it would be an excellent method whereby the practitioner could rapidly establish a diagnosis of syphilis. But less than half of the serums giving positive Wassermanns show coagulation with formalin, and—a fact of yet greater importance—nearly 10 per cent of nonsyphilitic serums give a positive result. Any claim to the reliability of the test is therefore demolished. As regards the Sachs-Georgi test the results obtained are distinctly promising. The technic is much simpler than that of the Wassermann on account of the omission of the complement and other constituents of the hemolytic system. But this is rather more than balanced by the great difficulty of determining the presence or absence of a precipitate in many instances. A strongly positive Sachs-Georgi reaction may be taken as evidence of syphilis, but a weak reaction must at present be looked upon with suspicion because of the difficulty in distinguishing between the weakest positive reaction and the slight precipitation given by some negative serums. It appears possible, however, that the detection of the weakest positives may be made easier by modification of the antigen and by special methods of reading the results.

**A Sign Occurring in Cases of Tabes Complicated by Charcot Joints.**—Leo Eloesser, San Francisco. *Journal of the American Medical Association*, 1921, vol. lxxvii, p. 604.

Some tabetics have an analgesia of the bone but not of the skin. This may be tested by thrusting a pin through the skin onto the bone. Such patients may

have pain following an acute development of a Charcot joint. Their pain is felt in the distended skin and soft parts, not in the bone. This kind of pain does not subvert the theory that Charcot joints are due to trauma plus a lack of the warning sense of pain. Pain fibers for skin and for bone probably run through the cord in different paths.

**Syphilis, Social Scourge, and Its Remedies.**—Queyrat (Paris), *Le Progrès Médical*, August 6, 1921, xlix, 32.

A sense of prudery still inhibits a properly aggressive antisymphilitic crusade, and recently at a gathering for the discussion of social maladies, syphilis was actually ignored. To get around this prejudice attempts have been made to coin new names for the disease, such as *Avarie* and *Treponemia*. But silence on syphilis is criminal. The public should know that thirty per cent of all hospital patients in medical services are ill with syphilis, largely of the vascular and visceral locations and central nervous system. In insane asylums, in addition to the paretics, many other inmates owe their plight to nervous syphilis. In pediatric clinics syphilitic manifestations are equally common and in maternity services we see much abortion and stillbirth, congenital syphilis, monstrous births, etc.

In the domain of prophylaxis early marriages are just now in vogue as the result of the war, and this custom, should it remain indefinitely, is one of the best safe-guards of the race. In the campaign of enlightenment, we should stress the fact that the generative organs are not "shameful" in themselves, more than others. Any of the higher organs can be devoted to "shameful" uses. Nor are there any microorganisms which are essentially "shameful," for any contagious disease can be contracted under immoral circumstances. The author is opposed to the prophylactic inunction so popular with the Americans, although it was introduced by Metschnikoff. His opposition is based on the fact established by himself that the calomel-thymol ointment does not destroy the treponema. The latter are only immobilized for the time and later resume their activity. However, in solution of mercury cyanate followed by thorough soaping, we have a certain spirilloicide. Other substances of the same power are 30 per cent alcohol, carbolic acid, sublimate, etc.

A solution of carbolic acid, 1 per cent in water, with alcohol addition of 20 parts to the thousand, is recommended as a prophylactic mouth wash and gargle. After contamination has occurred and the presence of an initial lesion noted, there is a period of 15 days in which prophylactic treatment may still be practiced. The seroreaction does not become positive until the 15th or 20th day, and during this period it may be possible to cure the case radically. In the meantime the ultramicroscope is used to detect the treponema and incidentally a research should be made for the bacillus of Ducrey. But it is at precisely this period when cure is possible that the patients—eighty per cent of them probably—consult the pharmacist who sells them an ointment or depurative. If something could be done to overcome this practice the problem of syphilis prevention would be much simplified. It is not until the appearance of the roseola that the pa-

tient turns to the physician. Whenever luckily the patient comes during the pre-Wassermann period he should always be treated with old salvarsan. There should be a course of eight injections, two the first and one each subsequent week, which occupies seven weeks; after which the patient should rest a month. The reaction should now be negative, but a second course of injections should be given. If the reaction remains weakly-positive mercury should be added to the arsenical treatment; if negative, mercury should be administered alone. The author prefers as a mercurial, argentic gray oil, which contains 20 per cent of impalpable powder of silver. Treatment is kept up off and on for a year; at the end of which time a provocative injection of salvarsan is given to determine the possibility of latent microbism. All seroreactions, including the intraspinal and Hecht's test should be negative.

The toxicity of salvarsan is known to be due to the content of "arsenoxide"—this is merely a contraction of a long synthetic term and not arsenious or arsenic oxide. In theory every preparation of salvarsan should first be tested on some animal but this is not always practicable. The author hopes that a method may be worked out on the rabbit and if the toxicity per kilogram is above the normal, the preparation should not be used on mankind. If there is any doubt about the existence of syphilis the salvarsan treatment should of course be withheld; we cannot use it for mere diagnostic purposes. This holds good for cases of possible mixed chancre.

Finally the sanitary chief of a locality should be appealed to in all cases in which the patient withdraws prematurely from treatment and in all other cases where the subject is a menace to the community—the untreated subject and the person of either sex who has sexual intercourse while infected. There should be no marriage without certificates of health and any infected pregnant women must submit to treatment.

**A. Consideration of Arsphenamine and Certain Other Organic Arsenic Compounds Used in the Treatment of Syphilis.**—George B. Roth, Washington, D. C. Public Health Reports, 1921, vol. xxxvi, p. 1990.

There is a well-marked individual variation in the susceptibility of animals to both arsphenamine and neoarsphenamine. Neoarsphenamine is so unlike arsphenamine in its biologic behavior that it should not be regarded as arsphenamine in a form convenient for administration. Acid solutions of arsphenamine are at least two to four times as toxic as properly alkalized solutions, the toxicity increasing directly with the concentration. The toxicity of properly alkalized solutions of arsphenamine is slightly less toxic as a 0.5 per cent than as a 2 per cent solution. The Ehrlich method of alkalizing arsphenamine, in which the monosodium salt is formed, produces a more toxic solution than the present method used in the United States, in which the disodium salt is formed. The use of impure sodium hydroxide should be avoided in making arsphenamine solutions. Increasing the rate of injection of properly alkalized arsphenamine greatly increases its toxicity. Properly alkalized arsphenamine solutions in many cases are more highly toxic immediately after the preparation than after

the lapse of about 20 minutes. Shaking alkaline aqueous solutions of arsphenamine and aqueous solutions of neoarsphenamine in the presence of air increases their toxicity markedly. Neoarsphenamine is a relatively unstable compound in sealed ampule and after an indefinite period may show changes in (1) color, (2) mobility in ampule, (3) solubility, (4) toxicity, and (5) odor. Difficulty or incompletely soluble preparations of neoarsphenamine may be highly toxic and should not be used clinically. In some cases neoarsphenamine in ampule may be rendered insoluble by incubation at 37° C. for about a year.

**Keeping Qualities of Market Samples of Neoarsphenamine While in Ampule.—**

George B. Roth, U.S.P.H., Washington, D. C., Public Health Reports, 1921, vol. xxxvi, p. 2523.

Commercial neoarsphenamine is a relatively unstable substance in ampule. Age, heat, and incomplete drying of the substance before ampuling are factors in causing deterioration in commercial neoarsphenamine. The deterioration of arsphenamine is shown by changes in color, mobility in ampule, toxicity, solubility, and odor. The results of the experiments suggest (a) that inasmuch as neoarsphenamine may deteriorate within a short time after manufacture, and in order to secure further data on its keeping properties, the date of manufacture might be given on the label of all lots issued; (b) that neoarsphenamine should be kept under conditions similar to those required for vaccines; that is, at ice-box temperature.

**Sulfarsenol in the Treatment of Congenital Syphilis.—**E. Crawford and G. B.

Fleming, Glasgow, Lancet, London, 1921, vol. cci, p. 700.

The results suggest that the intramuscular injection of sulfarsenol is not as efficacious in producing a cure of congenital syphilis, as evidenced by the Wassermann reaction, as intravenous injection of kharsivan. Whether the virtue in the latter method lies in the drug *per se* or in the method of administration (intravenous as against intramuscular) we are at present unable to say. On the other hand, the work of Harrison, White, and Mills seems to show that intramuscular injection of neosalvarsan or its substitutes is more efficacious in producing a negative Wassermann than intravenous injection of these drugs. In these cases, however, a very much larger dose was given intramuscularly than intravenously, and they did not attempt to determine the relative efficacy of the various arsenical preparations they used.

**The Treatment of Syphilis.—**H. S. Newcomer, Philadelphia. American Journal of the Medical Sciences, 1921, vol. clxii, p. 565.

It seems that the most striking information to be derived from a study of these statistics is that time plays a very important factor in the treatment of syphilis. The patients must have a certain amount of salvarsan, from 120 to 180 decigrams and its administration in appropriate doses must be spread over a considerable period of time. That factor in treatment which varies with

the stage of the disease is not so much the amount of salvarsan as the length of time over which it is to be administered. In primary and secondary syphilis the salvarsan should be administered within a period of about a year and results may be expected within the next half year. In tertiary syphilis the treatment is to be spread over a greater period of time, two to three years before results may be expected. These statements can only be considered as generalities. Individual patients vary greatly and furthermore no one would suppose that, having arrived at this point, the treatment should be stopped. Further treatment is advisable for all of these patients. How much and for how long future judgment must decide.

**The Treatment of Syphilis.**—Philip S. Smith, Abingdon, Va. *Virginia Medical Monthly*, 1921, vol. xlviii, p. 305.

The successful treatment of syphilis implies a correct diagnosis, proper laboratory controls, and the full co-operation of the patient. Mercury and arsphenamine are the most efficient drugs available for combating the disease. The ointment is probably the most active preparation of mercury for this purpose, and the intravenous use of neoarsphenamine is the most satisfactory method of administering arsenic in the average case of syphilis. With proper technic few reactions result. Iodides are of value chiefly in tertiary syphilis because of their alterative effects. Intraspinal treatment of chronic cerebrospinal syphilis with mercurialized and salvarsanized serum is advisable when other measures fail. No general rule can be offered as to the length of time treatment should be continued. Early syphilis, vigorously treated, is curable or controllable; in tertiary syphilis involving the central nervous system the prognosis is poor.

**Treating Syphilitics.**—Leo. L. Michel and Herman Goodman, New York. *New York Medical Journal*, 1921, vol. cxiv, p. 102.

The patient with syphilis, and not syphilis should be considered by the physician when it comes to treatment. The tissues of the patient are worthy of respect, especially when one considers that the assault of the drugs needed in treatment is added to the tissue damage of the spirochetes. Specific treatment of the syphilitic requires arsphenamine or one of its newer salts, neoarsphenamine, sodium arsphenamine, or silver arsphenamine. Mercury is also used in the specific treatment. The iodides are very valuable, especially in the later stages of the disease. The use of arsphenamine in the prophylaxis of syphilis is a phase in treatment that is very important, and its results make it worthy of wider use. Its share in the public health aspects of this disease are especially valuable. The intensive treatment in the early syphilitic, both when the abortive action and the quick and thorough sterilization of the patient seems feasible, is recommended for otherwise healthy persons with syphilis. Care in selection of the patient for this form of therapy is of first importance. Modified forms of injection of arsphenamine should be given according to the patient, the reactions of his excretory organs, response to drugs, and phase of the disease process. Iodides form a valuable addition, and the intravenous route should be considered,

especially if large doses by mouth tend to upset the patient. Systematic and systemic examination of the patient should be made at intervals, with especial reference to the cerebrospinal system. When indicated, the lumbar puncture for diagnosis and treatment is advised. Routine treatments in syphilis should be disregarded. Every syphilitic patient should be treated as an individual requiring attention, and not as a case of syphilis.

**Four Centuries in the Treatment of Syphilis.**—L. W. Shaffer, U. S. N. United States Naval Medical Bulletin, 1921, vol. xv, p. 749.

Over four centuries in the treatment of syphilis with mercury failed to develop any satisfactory standard of treatment. More than 10 years' experience in modern methods of treatment have likewise failed to bring us much nearer this goal. But advances have been made in this direction. At least the use of arsenicals and mercurials in association, with few exceptions, comprise the basis of modern systems of treatment. Time and observation of treated cases only will determine the mode of application, dosage, number of courses, and the length of periods of rest best applicable for cure. It is recognized that many syphilographers refrain from announcing a system of treatment, realizing that more is necessary than the simple 1-2-3 steps of system in piloting a given case to cure. It requires a thorough knowledge of the disease, a technical and therapeutic knowledge of methods of treatment, and the handling of complications that cannot be incorporated in a simple standard of treatment. Yet the writer strongly favors the adoption of some standard of treatment, at least for early cases of syphilis, in the United States Navy. There are several reasons for the adoption of such a standard. The service would benefit in the establishment of a standard for treatment whereby cases could be checked up and followed through a set course of treatment, barring complications, with less danger to the patient and more promise of cure, than where various standards are followed in the same case. More satisfaction among our patients would be produced by a standard treatment, and a better spirit of cooperation would be secured if they were not given various treatments according to the special leanings of different medical officers. Our records would be unified so that statistics could be compiled on a large number of treated and observed cases that would be, in future years, of the utmost value of such a standard and of present methods of treatment.

**Inefficiency of Intraspinal Treatment of Cerebrospinal Syphilis.**—P. F. Boffill (Colombia). *Revista Medica Cubana*, July, 1921, xxxii, 7.

The author relates a number of cases and draws conclusions as follows: The use of mercurialized and salvarsanized serums in the management of this location of syphilis, whether *in vivo* or *in vitro* is completely unsuccessful. Second, relative improvement attributed to this method, should not be reckoned, especially in regard to the use of salvarsanized serum *in vivo*, for there is no proof that salvarsan does not in these cases exert its action through escape into

the blood stream. Third, repeated puncture of the spinal canal exposes the patient to accidental complications of his disease. Finally, having noted that salvarsan may cause improvement in nervous syphilis after previous exhibition of intravenous injection of sodium iodide, the author is at present inclined to believe that this should be the treatment of choice, by no means forgetting that mercurial salts also have a role here; and he believes at the same time that intraspinal medication should be completely renounced.

**Present Opinion on Intraspinal Therapy in Neurosyphilis.**—Eugene N. Boudreau, Syracuse, N. Y. *Medical Record*, 1921, vol. c, p. 535.

The central nervous system is early invaded by the *Treponema pallidum*, and without necessarily giving clinical signs. Vigorous intravenous salvarsan treatment associated with mercury and the iodides removes the danger in a large number of cases. This must be confirmed by negative findings in the cerebrospinal fluid. Certain cases do not respond to this treatment alone. For these cases the best treatment so far devised, but not ideal, is by the Swift-Ellis-Ogilvie method, because various observers agree that clinical evidence is that in all but potential paretics the signs become negative if thoroughly carried out, and because both avenues of approach are employed. The method of Byrnes (mercurialized serum) is more dangerous and produces severe reactions. The drainage method of Dereum is not without danger, is extremely painful, and the results obtained by observers are not in agreement.

**Paresis Treatment by Arsphenamine and Mercury.**—Clarence A. Bonner, Worcester, Mass. *Boston Medical and Surgical Journal*, 1921, vol. cxxxv, p. 60.

The course of duration of the bedridden stage seems lessened by treatment, and dying patients in this stage do not linger so long in the usual wretched state. The serology bears no relation to remissions. The duration of ward life seems lengthened. The results are found to be favorable to treatment, but do not warrant a change in prognosis. Certain cases respond and others do not. No explanation is offered, unless it may be that the meningeal types, as have been reported, offer a better therapeutic opportunity.

**A Review of the Literature and a Discussion of Silver Arsphenamine.**—H. E. Michelson and David M. Siperstein, Minneapolis. *Archives of Dermatology and Syphilology*, 1921, vol. iv, p. 193.

The authors believe silver arsphenamine is a drug which has a marked effect on clinical manifestations of syphilis, when administered in smaller doses than is the custom with the other arsphenamines. Whether the effect is more profound and sterilization more thorough will require a longer period of observation to determine. Immediate reactions are about the same as with the other arsphenamines, and it is too early to speak with certainty of remote dangers. One must constantly bear in mind that silver arsphenamine is a more complex



salt than any other arsphenamines, and the physician must be on the alert for the slightest sign of intolerance. Its superiority over the other members of the group certainly is not so marked that a patient should in any way be jeopardized in order to receive this drug in preference to the other arsphenamine products. Although the drug is highly recommended by neurologists, nothing conclusive has been published indicating a selective action on neurosyphilis. It may be that the future treatment of syphilis will call for courses of the various arsphenamine products, each having its relative chronologic position.

**Studies Concerning the Influence of Arsenical Preparations on Cutaneous Tests.**—Albert Strickler, Philadelphia. *Archives of Dermatology and Syphilology*, 1921, vol. iv, p. 177.

The repetition of a luetin test in nonsyphilitic patients is capable of producing positive luetin tests in about 21 per cent of subjects. The intravenous administration of arsphenamine apparently stimulates the production of a luetin test in nonsyphilitic patients, and in series we were able to produce 53 per cent positive luetin tests following this form of intravenous specific therapy. In the author's experience the intravenous administration of cacodylate of soda acts in the same manner as arsphenamine only more feebly. The repetition of the tuberculin (von Pirquet) test may produce a positive finding, but very infrequently, occurring only once in this series of fourteen subjects. The intravenous administration of arsphenamine is capable of producing a positive tuberculin (von Pirquet) test, previously negative. This occurred in three instances in this series of ten patients. The anaphylactic food test made by either the endermic or scratch method does not seem to be influenced by the intravenous administration of either arsphenamine or cacodylate of soda. The author's investigation of this phase of the problem is, however, not yet complete. He is now engaged in studying the effect of the arsenicals given by mouth on the luetin, tuberculin and anaphylactic food tests.

**Experiences With Sodium Arsphenamine (Diarsenol).**—Henry E. Michelson and David M. Siperstein, Minneapolis. *Archives of Dermatology and Syphilology*, 1921, vol. iv, p. 184.

Sodium arsphenamine is a readily soluble, easily administered and safe preparation and exerts a marked influence on clinical manifestations of syphilis. The authors believe that courses of sodium arsphenamine should be supplemented with mercury. The therapeutic efficiency is apparently equal to that of the other arsphenamines (clinically). The effect on the Wassermann reaction is about on a par with that of the other arsphenamines.

## Correspondence

THE following letter issued by the Division of Venereal Diseases and sent to all State Venereal Control Officers is deemed of sufficient interest to reproduce in its entirety.—THE EDITOR.

Dear Doctor:

The inclosed circular in regard to the importance of continued treatment of persons infected with syphilis is recommended for your careful attention. It is believed that the subject matter is of sufficient importance to warrant this circular being reproduced and sent to each clinic in your State.

If you desire to send a copy to each clinic and have no facilities for reproducing the letter, a sufficient number of copies will be forwarded you upon your request.

By direction of the Surgeon General.

Respectfully,

C. C. PIERCE.  
Assistant Surgeon General.

December 30, 1921.

*To State Venereal Disease Officers and Others:*

Recent medical literature contains many expressions of opinion by Syphilographers, of this and other countries, regarding the high incidence and early onset of neurosyphilis. Another condition cited by them is that an increasing number of patients in the infectious second stage are being observed in the clinics. Many of the writers claim that too rapid sterilization and inadequate treatment are regarded as important contributory factors. Because of the seriousness of the problem and the diversity of opinion regarding the cause, the Service recently addressed a communication to a few of the leading syphilographers of this country asking for an expression of opinion on this important subject. The general opinion of the men written to is expressed as follows:

“While a certain amount of the apparent increase of neurosyphilis is due to the increasing use of spinal fluid examinations and other modern diagnostic methods, I think there is no question that the ineffective use of arsenicals plays a very important part in this most undesirable tendency \* \* \* the physician or health officer who is unable or unwilling to follow a syphilitic patient through a period of years, if not for life should not attempt to treat the disease. Relapse is certainly the great outstanding fact of syphilis and the so-called modern treatment has certainly not entirely done away with it. In particular, relapse in the nervous system and infectious involvement of the mucous membranes and genitalia are so alarmingly frequent under the inadequate use of arsphenamine that every agency which employs this drug in the treatment of syphilis should be thoroughly on the alert and equipped to detect the earliest manifestations of relapse.” (Stokes.)

“It appears to us that among the factors mentioned as probable causes, two are of paramount importance, viz., (1) the tendency to undertreat; (2) the failure to interpret pathologic findings in the light

of the clinical picture. (Fraser and Duncan, *British Journal of Dermatology and Syphilis*, July, August and September, 1921). To these we would add another of almost equal importance—the tendency to interrupt treatment by periods of rest. To our minds the treatment of all syphilis ought logically to be continuous rather than intermittent. Early neurosyphilis in the form of neurorecurrences would be reduced to nil if this were done. Late clinical neurosyphilis might be equally easily avoided by the early routine use of spinal puncture and by adjustment of treatment to the pathological findings. We agree that the ‘sterilization’ treatment of syphilis, as exemplified by Pollitzer’s method, is distinctly dangerous from the point of view of neurosyphilis, and that treatment should be directed toward building up the patient’s own resistance to the disease. Stokes’ discussion of this problem in his paper ‘The Application and Limitation of the Arspenamine in Therapeutics’ (*Archives of Dermatology and Syphilology*, September, 1920—See Venereal Disease Division Abstracts, March, 1921) deserves wider circulation than it has as yet obtained. The most crying present need of syphilotherapy is a standard treatment, sufficiently elastic to be adapted to all types of cases, and sufficiently simple to be used by the average physician . . . unless a physician feels himself competent to carry out all the necessary procedures in the treatment of any given case, he should not attempt to treat it at all. Though many cases can be successfully dealt with by the general practitioner, he should realize that the appearance of any complicating features is sufficient to warrant the transfer of the patient to a competent syphilologist.” Keidel and Moore).

“Syphilis of the nervous system probably begins in the first year of the infection. The number of cases corresponds roughly with the total number of cases of so-called late neurosyphilis. These statements are based on the following observations:

(a) The number of early cases showing positive findings in the spinal fluid; (b) familial types of neurosyphilis; (c) biologic evidence of a neurotropic strain of the treponema; (d) persistence of the infection in loco, as in aortitis, interstitial keratitis, etc.; (e) observation of patients who developed signs of early syphilis of the nervous system and who after many years died of paresis or other late degenerations; (f) no serologic evidence as yet exists showing normal spinal fluid in the early stage and its infection at a later period.

Early neurosyphilis may manifest itself by obtrusive symptoms, by slight objective signs or be asymptomatic. Unless they are properly and thoroughly treated these early infections may persist and cause late neurosyphilis.

Every case of early syphilis should be treated intensively with arsphenamine and mercury given systematically in courses consisting of not less than eight injections of arsphenamine or its equivalent, neoarsphenamine or silver arsphenamine, and fifteen injections of mercury; a minimum of two courses of the former and three of the latter should be administered. The treatment should be controlled by frequent Wassermann tests and a lumbar puncture made about six months after infection or earlier if indications should exist. Complete neurological examination should be made in order to detect early involvement of the nervous system and as a control for future examinations.

The treatment outlined is not an insurance against the occurrence of neurosyphilis which not infrequently takes place during the ac-

tive administration of the drugs. In such cases intraspinal medication administered by one familiar with the proper technic may be a necessary adjunct. It is only by controlling early neurosyphilis that we can hope to prevent the later degenerations.' (John A. Fordyce.)

It is of extreme importance therefore that physicians engaged in the treatment of syphilis carefully consider these statements and direct treatment toward the avoidance of the dangers outlined.

In inviting your attention to this matter the Service is not unmindful that many clinicians are engaged in the control of venereal disease merely from the standpoint of health officers, and that available funds do not admit of intensive or long continued treatment and are often used for sterilization purposes for public health protection. That there is danger to the public health in dismissing patients from treatment too early is seen in the claims of some observers who state that as larger numbers of infected individuals are brought under surveillance opportunity is afforded to observe an increased number of patients in the infectious second stage, which condition they believe to be due to inadequate treatment.

In the light of present knowledge regarding the subsequent danger to both the individual and community by ineffective and inadequate treatment, the Service urges that great care be exercised in recording case histories; in referring patients for intensive treatment to health centers or competent physicians to continue treatment when the clinic is unable to do so; and keeping cases of positive syphilis under proper observation, until the period of danger for both the individual and the community has passed.

By direction of the Surgeon General.

Respectfully,

C. C. PIERCE,  
Assistant Surgeon General.

## BOOK NOTICES

(Books for Review should be sent to Dr. W. H. Deaderick, Associate Editor,  
Dugan-Stuart Bldg., Hot Springs, Arkansas.)

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### SYPHILIS AND VENEREAL DISEASES, FOR STUDENTS AND PRACTITIONERS.

—By C. F. Marshall, M.D., M.Sc., F.R.C.S., Formerly Assistant Surgeon to the Hospital for Diseases of the Skin, Blackfriars, and Resident Medical Officer to the London Lock Hospital, and E. G. French, M.D., Ch.B., F.R.C.S. Edin., Lieut-Col. R.A.M.C. (Retired), Late O.C. Military Hospital, Rochester Row, London, and 51st and 56th General Hospitals for Venereal Diseases, France. Numerous illustrations and seven colored plates. Fourth edition. 433 pages. New York, Wm. Wood & Co., 1921. Price \$6.00.

Three hundred thirteen pages of this book are devoted to syphilis. Chapters are devoted to laboratory diagnosis, the primary lesion, the various systems affected and to treatment. The description of inherited syphilis covers nearly sixty pages. The various methods of intraspinous therapy are described and commented upon. The consideration of silver salvarsan and sulpharsenol testifies to the recentness of the revision. A monograph that can survive four editions has much to recommend it which is the case with this work.

**A PRACTICAL TREATISE ON DISEASES OF THE SKIN.**—By Oliver Ormsby, M.D., Professor and Head of the Department of Skin and Venereal Diseases, Rush Medical College, Dermatologist to the Presbyterian, St. Anthony's and the West Suburban Hospitals; Consulting Dermatologist to the Orphan Asylum of the City of Chicago, etc. Second Edition, Thoroughly Revised, 1166 pages. Illustrated with 445 Engravings and 4 Plates in Colors and Monochrome. Lea and Febiger, Philadelphia and New York, 1921. Price \$10.00.

In the reconstruction of the second edition of this book approximately four hundred pages have been rewritten, fifteen new dis-

eases described, and the entire work brought up to date. Many of the older illustrations have been replaced and the magnificent engravings are probably the outstanding feature of this work, adding much to the written descriptions. Many skin lesions in the negro are illustrated enhancing the value of the book to those treating skin diseases among this race. This is unquestionably one of the best monographs on dermatology which has appeared for years.

# The American Journal of Syphilis

A QUARTERLY JOURNAL DEVOTED TO THE  
STUDY AND PREVENTION OF SYPHILIS

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VOL. VI.

ST. LOUIS, APRIL, 1922

No. 2

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## Original Articles

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### COMPARATIVE CLINICAL OBSERVATIONS ON INVOLVEMENT OF THE NERVOUS SYSTEM IN VARIOUS PHASES OF SYPHILIS\*

BY JOHN H. STOKES, M.D.,

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(Received for publication, March 1, 1922)

IN THE course of a systematic study of a series of 231 cases of early syphilis seen in the Section on Dermatology and Syphilology of the Mayo Clinic since its organization in 1916, interesting observations developed which, while they do not break entirely new ground, are still too little familiar to the profession at large. It is not our intention to discuss in this paper the literature of neurologic changes associated with early syphilis. We submit, however, a table (Table I) in which are summarized a number of published

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\*From the Section on Dermatology and Syphilology, Mayo Clinic.

TABLE I  
STATISTICS ON INVOLVEMENT OF THE NERVOUS SYSTEM IN VARIOUS PHASES OF SYPHILIS

DATE	AUTHOR	PHASE OF SYPHILIS	PER CENT OF CASES									
			CASES	POSITIVE BLOOD WASSERMANN	ABNORMAL SPINAL FLUID	POSITIVE SYMPTOMS	POSITIVE SIGNS	SPINAL FLUID FINDINGS				
								WASSERMANN REACTION POSITIVE	INCREASED GLOBULIN	PLEOCYTOSIS	GOLD-SOL TEST	
1913	Altman and Dreyfus	Secondary	36		78.0							
1915	Wile and Stokes	Secondary	36		66.7							
1915	Nonne quoted by Southard and Solomon	Paresis Tabes		95-100 60-70								
1917	With	Secondary, early	212		26.0							
1917	With	Secondary, recurrent	15		80.0							
1917	With	Paresis	20		100.0				100	95-100	95	
		Gumma of the central nervous system	15		80.0							
		Tabes	19		52.0							
1917	With	Congenital, late	26		38.4				8		29	
1919	Fildes and others	Secondary, duration six months	85						100	100	100	
1919	Fordyce	Tabes	21	81.0	100.0				100	100	25 Zone 1 Zone 2	
		Paresis	40	95.0	100.0				100	100	100 Zone 1	
1919	Jeans	Congenital	214	99.1	32.7	16			97	100	98	
1920	Miller	Paresis		97-100					60-89	90-95	85-90 Zone 1	
	quoted by Craig	Tabes		70.0					85-90	90-95	85-90 Zone 2	
		Cerebrospinal		70-80							85-90 Zone 2	



TABLE I—CONTINUED

DATE	AUTHOR	PHASE OF SYPHILIS	PER CENT OF CASES								
			SPINAL FLUID FINDINGS								
			CASES	POSITIVE BLOOD WASSERMANN	ABNORMAL SPINAL FLUID	POSITIVE SYMPTOMS	POSITIVE SIGNS	WASSERMANN REACTION POSITIVE	INCREASED GLOBULIN	PLEOCYTOSIS	GOLD-SOL TEST
1921	Stokes and McFarland	Primary and secondary, early, untreated	114	82.0	44.0	16		14	33	95	25 Zone 1 45 Zone 2
1921	Fordyce and Rosen	Secondary, late, treated	243	48.0	26.0*	53	64	89	100	100	35 Zone 1, 53 Zone 2
1921	Wile and Marshall	Latent		100.0†	28.0						
		Late, involvement of skin, bone, and viscera			30.0						
1921	Gennerich	Tabs and myelitis		60-70 less after tenth year							
				90.0							
1921	Stokes and Brehmer**	Neurorecurrences In railroad men and farmers	200	45-50	65.0		65				
1921	Stokes and Busman	Wasserman fast, treated cases	100	100.0	43.0		43				
1921	Kingery	Congenital	52		28.8			90		100	
1922	Stokes and Brown**	Syphilites with "stomach trouble"	200	44.0	59.0						

\*The authors give 38 per cent. The 26 per cent result fits in with the methods used throughout our work.

\*\*This is essentially the syphilis of a medical and surgical diagnostic clinic where the spinal fluid examination forms a part of the routine special investigation for syphilis.

statistics on the spinal fluid findings in various phases of the disease and in different types of patients.

In interpreting the differences between the results of various investigators, a number of considerations which are only too easily overlooked must be considered. The high proportions of abnormal spinal fluids in early syphilis as they appear in the first items of Table I were the results of punctures on untreated patients. Contrary to the general belief, the spinal fluid in early syphilis makes a very rapid response to even moderately effective treatment. The proportion of abnormal spinal fluids falls rapidly from 60 per cent before treatment to 40 per cent after two or three arsphenamine injections, and after one or more courses of six injections drops to the 25 to 30 per cent obtained by Fordyce in his various statistical studies. We found for example in our own series, that when the first Wassermann test on the blood and the examination of the spinal fluid were separated by an interval of one month (four arsphenamine injections) or less, the percentage of abnormal spinal fluids stood at 44, while if four months or more elapsed (equivalent to at least eight arsphenamine injections and forty inunctions) the percentage fell to 36. Wile and Marshall find, in latent cases, 28 per cent with spinal fluids positive to the Wassermann reaction. Fordyce and Rosen give a published estimate of 38 per cent in their most recent study, but this apparently is the result of computing the percentage relation which the abnormal spinal fluids bear to those negative, rather than the positive spinal fluids to the total number examined, as in our percentages. If their results are computed on the same basis as ours, only 26 per cent positive spinal fluids will be obtained in their late secondary syphilis. That this still lower percentage is an expression of the longer duration of the infection and the more extensive treatment which their patients received prior to the spinal fluid examination, appears from a critical examination of our two groups of data. Similar comparisons of data on other aspects of syphilis in which results by various authors disagree would probably provide a similar basis for reconciliation of apparently conflicting conclusions. In Table II our patients are compared with those of Fordyce and Rosen.

It is apparent that a much larger proportion of our patients had

TABLE II

COMPARISON OF TWO GROUPS OF PATIENTS WITH SECONDARY SYPHILIS WITH SPECIAL REFERENCE TO AMOUNT OF TREATMENT RECEIVED BEFORE EXAMINATION

	ABNORMAL SPINAL FLUIDS PER CENT		NEGATIVE SPINAL FLUIDS PER CENT	
	Less than one course of treatment	More than one course of treatment	Less than one course of treatment	More than one course of treatment
Fordyce and Rosen	30	70	21	79
Stokes and McFarland	67	33	62	38

received very little treatment at the time of the first examination of the spinal fluid, than have those in Fordyce and Rosen's series. In fact the patients who have received less than one course in our series were almost all punctured after their first arsphenamine injection. The same difference between the series develops when duration of infection is compared (Table III).

TABLE III

COMPARISON OF TWO GROUPS OF PATIENTS WITH SECONDARY SYPHILIS WITH SPECIAL REFERENCE TO DURATION OF INFECTION

	ABNORMAL SPINAL FLUID PER CENT			NORMAL SPINAL FLUID PER CENT		
	Less than six months	Less than one year	More than one year	Less than six months	Less than one year	More than one year
Fordyce and Rosen	17	56	44	35	67	33
Stokes and McFarland	70	90	10	68	86	14

From this comparison it is evident that not only in treatment, but in duration, our series represents a fresher type of secondary infection than that of Fordyce and Rosen. With this point established, we shall proceed to a discussion of our individual findings, comparing them first with those of Fordyce and Rosen's recent series of late secondary cases and then with the results in our own and Fordyce and Rosen's surveys of the interrelation between blood and spinal fluid findings in early and late syphilis.

An interesting comparison of the individual elements of the

TABLE IV

COMPARISON OF POSITIVE FINDINGS IN SPINAL FLUID IN PATIENTS WITH EARLY AND LATE SECONDARY SYPHILIS

SPINAL FLUID FINDINGS	STOKES AND MCFARLAND EARLY (PER CENT)	FORDYCE AND ROSEN LATE (PER CENT)
Positive Wassermann reaction	14	89
Globulin increased	33	100
Pleocytosis	95	100

spinal fluid findings in early and late secondary syphilis in the two series is tabulated in Table IV.

Nothing could better express the meningeal character of early neurosyphilitic involvement than these data in which the cell count is increased in nearly 100 per cent of early cases, but the positive Wassermann reactions and globulin estimations lag considerably,\* only catching up with the cell count when the neurosyphilitic process is fully established and the parenchyma involved. We should point out, however, that our proportion of positive Wassermann reactions would be somewhat higher had 1 c.c. of fluid been used from the outset instead of 0.5 c.c. as in a few of our earlier cases.

An interesting observation on the relative frequency of Zone 1 and Zone 2 colloidal gold tests in early and late secondary syphilis can be drawn from these two series, although the number of our cases was too small for results to be conclusive. The ratio of Zone 1 to Zone 2 gold-sol curves is only very slightly greater in the late cases than in the early relatively untreated secondary cases. If the gold-sol test has much prognostic significance, it suggests that the unfavorable trend of certain cases with early neurosyphilitic involvement must be established comparatively early in their course, and the proportion of Zone 1 to Zone 2 curves stays fairly constant through the early period of the disease. Further observation would be needed to evaluate this suggestion.

The relation of early to late secondary syphilis, in the matter of development of symptoms suggestive of neurosyphilitic involvement, is of some interest. Only 16 per cent of our series of patients with abnormal spinal fluids had symptoms of any description which might

\*This same point is well brought out by the observations of Fildes, Parnell and Maitland, in which, in early cases, the positive Wassermann reaction lags well behind the pleocytosis.

suggest the existence of cerebrospinal changes. Fordyce and Rosen, dealing with later secondary cases, found that 53 per cent of their patients with spinal fluids giving positive Wassermann reactions had developed symptoms suggestive of neurosyphilitic changes. They found, moreover, that 64 per cent had objective neurologic signs. Unfortunately, detailed neurologic examinations were made on only a few patients in our series, so that we have no comparative data on this point. We may safely say, however, that neurologic signs are suggestive of a fully established, not an early or incipient process. The statistics of Fildes, Parnell and Maitland confirm this view. It was evident from individual cases in our series that there is no necessary relation between the grade of abnormality shown by the spinal fluid and the symptoms. Evidently symptoms do not necessarily arise from the meninges, for a severe meningismus may be present with an almost negative fluid (for example, Wassermann negative to 1 c.c., Nonne negative, 7 lymphocytes) while a patient with a severe meningitis (Wassermann negative to 0.5 c.c., Nonne positive, 328 lymphocytes) may have only a mild headache. Headache and meningismus may both be present in a patient with only moderate involvement, as shown by the spinal fluid (Wassermann positive with 0.4 and 1 c.c. Nonne positive, 30 lymphocytes). It is evident, therefore, that the clinical course of a case, in the early months of the disease, cannot serve at all as a guide to the identification of neurosyphilitic changes, or be used as a substitute for examination of the spinal fluid. The earlier the case the fewer the symptomatic clues, and yet the better the prognosis under intelligent treatment. The syphilographer who carries the treatment of his primary and secondary cases into their second course without examination of the spinal fluid is proceeding blindfolded. He is doing worse, for, as several of our cases illustrate, serious grades of neurosyphilitic involvement indicated by the spinal fluid may occur before the appearance of secondary lesions, to say nothing of general symptoms, and may fail to respond to a single routine course of treatment. If the patient is then discharged with an incipient neurosyphilis, or is placed on a less intensive interim mercurial treatment, the danger of a neurorecurrence is very great. We have been called on quite frequently to deal with such neurorecurrences following short courses or even fairly intensive courses given by

other physicians, in which examination of the spinal fluid was not made before the patient was temporarily discharged. Indifference to the necessity for such an examination before the end of the first course of treatment is probably responsible for the increasing incidence of alarming accidents, particularly involving the cranial nerves, which are bringing modern syphilotherapeutic methods into disrepute.

Several striking examples of the course of early neurosyphilis observed in our series deserve brief descriptions, for example:

URETHRAL CHANCERE. NO SECONDARIES. INVOLVEMENT OF THE NERVOUS SYSTEM EVIDENCED BY MENINGEAL REACTION (LYMPHOCYTES 102), DETECTED AS A RESULT OF ROUTINE SPINAL PUNCTURE BEFORE DISMISSAL  
MRS. P. B., HOUSEWIFE, AGED FORTY YEARS

3/11/19 Examined.

No general complaint: irritation on urinating.

Induration at urinary meatus, hard, almost stony.

*Tentative Diagnosis:* carcinoma.

*Wassermann Reaction on the Blood:* strongly positive.

*Dark-field Examination* made after Wassermann reaction was positive for *Spirocheta pallida*.

*Revised Diagnosis:* urethral chancre, no secondary eruption.

*Treatment:* arsphenamine intravenously, three injections.

*Threatened Exfoliative Dermatitis.*

*Arsphenamine* continued under alkalization to seven injections.

*Routine Spinal Puncture* before beginning interim mercurialization yielded the following:

*Spinal Fluid Examination:* Wassermann reaction negative, Nonne test positive, 102 lymphocytes, gold-sol test negative.

*Intensive Intramuscular Mercurialization* begun.

Sodium iodide intravenously 140 gm.

*Prompt and Satisfactory Response.*

*Spinal Fluid Normal Before Discharge* and six months later.

#### DISCUSSION

1. *High Grade Meningeal Involvement* may anticipate the appearance of secondary lesions.
2. *There is no Necessary Parallelism* between the patient's symptoms and the spinal fluid findings.
3. *The Spinal Puncture Should Therefore Be Routine* and not optional.
4. *A Severe Neurorecurrence Was Undoubtedly Prevented* in this case by the routine puncture before the patient was released to less intensive treatment.
5. *The Meningeal Involvement in This Case Was Completely Controlled* by mercury and intravenous sodium iodide.
6. *Note That the Wassermann Reaction* has always been negative on the spinal fluid.
7. *Urethral Chancres at the Meatus in Women* because of their stony hardness are often suspected of being carcinomas.

OPTIC NEUROCURRENCE WITH NORMAL SPINAL FLUID AND BLOOD FOLLOWING  
INSUFFICIENT ARSPHENAMINE TREATMENT. RAPID RECOVERY AND APPAR-  
ENTLY COMPLETE CURE. REINFECTION (?) (PRIMARY AND SECONDARY  
LESIONS) FOURTEEN MONTHS AFTER FIRST EXAMINATION

MR. P. G., LABORER, AGED THIRTY-TWO YEARS

7/28/20 Examined.

*History of Penile Lesion* with secondaries six months before.

*History of Treatment:* five intravenous arsphenamine injections and potassium iodide by mouth, no mercury.

*Vision Began to Fail* one month after last arsphenamine injection.

*Eye Examination:* violent rapidly progressing neuroretinitis.

*Physical Findings* negative.

*Wassermann Reaction on the Blood* negative.

*Spinal Fluid* negative.

*Diagnosis:* neuroretinitis, probably syphilitic.

*Rapid Improvement* under mercury succinimid and iodide followed by arsphenamine.

*Further Treatment:* four arsphenamine courses as for an early infection. Forty injections of mercury succinimid, 200 four-gram inunctions, 325 gm. sodium iodide intravenously.

11/22/21 *Reexamined:* multiple penile lesions developing two weeks after a drunken spree.

*Physical Findings:* several scattered papules on penis of several weeks' duration.

*Induration of Old Scar:* no erosion or other sign of activity.

*Spirocheta Pallida* demonstrated eight days after examination in small penile lesion.

*Wassermann Reaction on the Blood* strongly positive.

*Maculopapular Secondaries on Trunk and Arms Appeared Twenty Days After Examination.*

*Wassermann Reaction on the blood* again strongly positive.

*Condition of the Eyes:* normal except for organized exudate of healed neuroretinitis.

*Spinal Fluid* negative.

12/27/21 *Wife Seen With Chancre of the Cervix.*

#### DISCUSSION

1. *Grave Involvement of a Cranial Nerve* in the neurorecurrences of early syphilis, may be associated with a negative Wassermann reaction on the blood and negative spinal fluid.
2. *It is Remotely Conceivable That the First Neuroretinitis Was Nonspecific*, but its rapid response to mercury (succinimid and iodide with the history would seem to establish the first syphilitic infection.
3. *Was the Second Infection a Relapse (Monorecidive), a Reinfection, or a Superinfection?*

The induration of the old primary scar suggests a relapse. On the other hand, spirochetes could not be found in this induration, but they were demonstrable in one of the chancres at a distance from the original lesion. While specific exposure was denied, the patient had been drunk and irresponsible at approximately the proper time for a new infection to have occurred. It is not possible, however, to state categorically that this is not a primary relapse with a second crop of secondaries.

4. *Reinfection Cannot Be Proved* without a more definite history of exposure and a chancre less obviously in the immediate neighborhood of the original primary.
5. *A Superinfection is Easily Conceivable* but not probable in this case.

6. *The Course of the Second Infection Has Been Very Different From the First.* No tendency to involve the optic nerve is thus far apparent.
7. *If This is a Relapse of the Original Infection* the original involvement of the optic nerve (neurorecurrence) would scarcely appear to be due to a neurotropic strain of organism, but rather to the effect of insufficient treatment (especially lack of mercury as such).

The prognosis from the standpoint of neurosyphilitic involvement of the patient whose spinal fluid at the first examination is found to be entirely normal, is a matter of much importance. Wile and Marshall and others have found that a patient whose spinal fluid is normal after his secondary eruption has developed, is not likely subsequently to exhibit involvement of the nervous system. Our experience in this series of cases confirms this point. Of 114 patients of whom the necessary data were available, only four whose spinal fluids had been normal at the first examination subsequently developed abnormal fluids. This accords with the suggestions derived from the comparison of our data with those of Fordyce and Rosen, in which the general statistical findings indicate that the percentage incidence of neurosyphilis, while high at first, settles to a fairly constant figure comparatively early, within the first two years of the course of the disease.

The work of Weed describing the production of meningitis by spinal puncture during meningococcus septicemia has made us feel that there is at least theoretic danger of a transfer of organisms from the blood to the meninges with the development of a syphilitic meningitis in the patient subjected to premature puncture during his spirochetemic stage. We have, therefore, made it a rule never to do a spinal puncture in early syphilis until the patient has had one or two injections of arsphenamine to bring his spirochetemia under control. In later cases the puncture is usually made with the second arsphenamine injection. We undoubtedly miss some of the minor changes in the fluid in this way, especially in the early cases, but we believe the precaution is worth while.

In Table V are presented the results of a comparison of blood and spinal fluid findings in four series of observations, two by Stokes and McFarland, and Stokes and Brown and two by Fordyce and Rosen.

The data in Table V support some interesting generalizations. It should be borne in mind that the first column contains the results in



TABLE V

A COMPARISON OF THE INTERRELATIONS OF BLOOD AND SPINAL FLUID FINDINGS  
IN PATIENTS WITH VARIOUS TYPES OF EARLY AND LATE SYPHILIS

BLOOD WASSERMANN REACTION	SPINAL FLUID	SECONDARY SYPHILIS, PER CENT		LATE SYPHILIS PER CENT	
		EARLY, STOKES AND MCFARLAND	LATE, FORDYCE AND ROSEN	STOKES AND BROWN	FORDYCE AND ROSEN
Positive	Negative	40	26	23	22
Negative	Negative	16	47	18	16
Positive	Positive	36	21	18	48
Negative	Positive	8	5	41	14

very early, relatively untreated syphilis. The second column applies preponderantly to late, largely treated secondary syphilis. The third column represents the syphilis of medical and surgical practice based on findings in 200 syphilitic patients who entered the Mayo Clinic without a diagnosis and with a chief complaint of "stomach trouble." The fourth column represents the experience of a syphilographer known by the profession to give much of his attention to neurosyphilis, and for that reason presumably the recipient of referred cases in which the diagnosis of syphilis by the referring physician is often based on the finding of a positive Wassermann reaction on the blood. In these types of syphilis and varieties of practice the following features seem to stand out:

*Wassermann Reaction on the Blood Positive, Negative Spinal Fluid.* This type of case is most common in early untreated syphilis (40 per cent). After the first to the second year the percentage drops to 26, with a further slight but not marked decline during the subsequent years of the infection. It is rather interesting that, in a practice such as that of Fordyce, only one-third of the patients with late syphilis whose blood is positive to the Wassermann reaction should have negative spinal fluids. The existence of about 60 per cent of patients whose spinal fluids are positive to the Wassermann reaction certainly suggests the need for using the examination of the spinal fluid as a complement to the Wassermann test on the blood in all properly equipped consultant diagnostic practices.

*Wassermann Reaction on the Blood Negative, Negative Spinal Fluid.* In untreated cases this group of patients remains so strikingly constant throughout the course of the disease as to suggest that

these relatively fortunate patients are selected from the earliest days of their infection. The proportion of blood and spinal fluid that is normal can evidently be greatly increased by even a moderate amount of good treatment, applied within the first two years of the disease. The need, therefore, for an accurate diagnosis of early neurosyphilitic changes as a guide to what is required for effective treatment in the individual case, is the more apparent. It should be recalled also, that in late syphilis, serologically negative cases belong quite often in the vascular, tabetic crisis, and other special groups of active neurosyphilis.

*Wassermann Reactions on the Blood Positive, Spinal Fluid Positive.* Patients of this type are fewer among early treated cases than in untreated cases of corresponding duration, obviously as a result of treatment. To us the most interesting aspect of this part of the table is the striking difference between our own results and those of Fordyce and Rosen in the case of late syphilis. Three factors, we believe, combine to explain this discrepancy between 18 and 48 per cent. In the Mayo Clinic the examination of the spinal fluid is used more freely in making or eliminating the diagnosis of syphilis than in the majority of personal practices, and in many diagnostic groups. The Wassermann test on the blood alone, must, for the majority of physicians, be the chief criterion on which a diagnosis is based. They accordingly overlook a certain percentage of cases in which the reaction on the blood is intrinsically negative; this percentage has been estimated by Gennerich to be as high as 30 to 40 per cent in tabes after the first decade. Those who in ordinary practice send their syphilitic patients to a consultant such as Dr. Fordyce, are perhaps apt artificially to select his cases for him on the basis of the finding of a positive Wassermann reaction on the blood. On the other hand, it is our experience that not a few of our patients come to us after they have had some treatment by the home physician or by other specialists, so that a certain proportion, whose blood has been rendered normal by this means, show only positive findings on examination of the spinal fluid, which, in the later stages of syphilis, is much more resistant to treatment than in the earlier. Between these three factors (the last of which has been to some extent analyzed by Stokes and Brown) there is abundant explanation for the relatively low percentage of Wassermann positive bloods which we obtain in our patients with positive spinal

fluids. At first we were disposed to attribute this low percentage to a Wassermann test less sensitive than that used by Fordyce, but it appears from the study of our Wassermann test in cases of florid secondary syphilis, and from a study of its relation to previous treatment that our Wassermann test should yield, under unmodified conditions, practically the same percentage of positives as does Fordyce and Rosen's. Under the circumstances, then, we are both right, and the fact illustrates how complex may be the influences which affect conflicting estimates of this or that aspect of disease.

*Wassermann Reaction on the Blood Negative, and Positive Spinal Fluid.*—Our results as expressed by these percentages have now been borne out by several surveys, so that from our experience we feel safe in accepting them as valid. The difference between 41 per cent with negative bloods in our series and 14 per cent in Fordyce and Rosen's must be again explained by the considerations advanced in the preceding paragraph. We feel convinced that apart from the "factitial" elements, there exists a group of patients, considerably larger than is suspected in routine practice, whose blood will be negative to the Wassermann reaction but whose spinal fluid will present proof of the presence of neurosyphilis. These cases may present neurologic signs, and especially pupillary changes, which will assist in their recognition in a routine general examination. On the other hand, there will be a proportion, not exactly estimable as yet, which will not present neurologic signs, yet will be latent neurosyphilis, as shown by examination of the spinal fluid. The detection of this group of cases, the demonstration of their diagnostic importance and their treatability will devolve on those who examine the spinal fluid for diagnostic purposes as part of the general examination of patients who present any ground whatever for the investigation of syphilis as a factor in their condition. We are inclined to estimate the proportion of positive spinal fluids in spite of negative bloods as from 25 to 30 per cent in routine diagnostic work involving late syphilis.

#### SUMMARY

A comparative study of the results of spinal fluid examination in four groups of syphilitic patients, two with early and late secondary syphilis (Stokes and McFarland, Fordyce and Rosen), one representing a cross section of internal medical work in the Mayo

Clinic (Stokes and Brown), and one of late syphilis in a consultant syphilologic practice (Fordyce and Rosen) yields the following conclusions.

1. Treatment and time are important factors in the statistical estimates of the proportion of abnormal spinal fluids in syphilis. In very early untreated secondary cases the proportion of positive findings, specific and nonspecific, may reach 60 to 70 per cent, falling to 40 per cent within the first six months, and to 25 or 30 per cent after the first year or two. From this time on the decline is more gradual.

2. Treatment of incipient neurosyphilis within the first two years, if intensive, causes a rapid and marked response in many cases. Even relatively ineffective treatment causes temporary gains and a certain degree of spontaneous involution may perhaps also be expected. This is, therefore, the period on which our best therapeutic energies should be concentrated.

3. The rise in cell count evidencing meningeal reaction is the earliest and commonest change in the spinal fluid in secondary syphilis in our experience. While not necessarily specific for syphilis of the nervous system, it is safer to regard it as an evidence of early syphilitic meningitis and treat it accordingly than to disregard it. This meningeal reaction is followed by an increase in globulin content and, finally, by a positive Wassermann reaction. The use of considerable amounts of spinal fluid in the Wassermann test is essential at this stage in order to detect the positive Wassermann on the spinal fluids.

4. There is no parallelism between early symptoms and spinal fluid findings which can be safely used as a guide to the advisability of examination of the spinal fluid. The examination should, therefore, be made routinely.

5. Symptoms and signs are to be regarded as late rather than early manifestations of involvement of the nervous system. Only 16 per cent of early cases showed symptoms, as against 53 per cent in late secondary cases.

6. The routine examination of the spinal fluid early in the first course of treatment (second or third arsphenamine injection) will give a valuable guide to the therapeutic indications in individual cases. It is preferable to later examination of the fluid.

7. A patient with early syphilis under combined arsphenamine

and mercurial treatment should not be discharged from a first course of treatment, or be placed on mercurialization alone without an examination of the spinal fluid. Even a slight pleocytosis may be a warning of meningeal involvement which will flare up in a neuro-recurrence if treatment is relaxed or suspended.

8. Spinal puncture, we believe, should not be done in primary and secondary cases, early or late, without a preliminary sterilization of the blood stream by one or two arsphenamine injections to prevent a possible transfer of organisms to the meninges.

9. Patients whose spinal fluid is normal during the early secondary period, show a distinct immunity from subsequent involvement especially if effective treatment is carried on. Neurosyphilitic involvement apparently takes form comparatively early in the course of the disease. A proportion of patients ranging from 40 to 50 per cent will have normal spinal fluid at all stages.

10. The proportion of patients who have normal spinal fluid can be increased apparently 50 to 75 per cent over the average in early and late cases by effective treatment during the first two years of the disease. This is, then, the vital period of the disease from the therapeutic standpoint.

11. The spinal fluid findings in both early untreated and late syphilis show a group of 16 to 18 per cent whose blood and spinal fluid appear normal.

12. A proportion of patients varying from 5 to 8 per cent in early syphilis and from 14 to 41 per cent in late syphilis will present negative Wassermann reactions on the blood and abnormal spinal fluids. The proportion of patients with this important diagnostic combination will vary in different series with the duration of the infection, previous treatment, the character of the clientele, and the freedom with which the examination of the spinal fluid is used in the investigation of a clinical suspicion of syphilis.

13. As a syphilitic infection progresses from the early to the late stages and as the form of involvement gives rise to symptoms, neurosyphilitic changes assume increasing importance. To a surprising degree neurosyphilis complicates or underlies the internal medical aspects of the disease. In its detection the examination of the spinal fluid may exceed any other single procedure in diagnostic importance and proportion of positive results. In the diagnostic work of the Mayo Clinic, for example, a proportion of only 45 to

50 per cent positive Wassermann reactions on the blood as compared with 60 to 70 per cent positive Wassermann reactions on the spinal fluid of syphilitics seems to be the rule.

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## THE MARYLAND STATE DEPARTMENT OF HEALTH VENEREAL DISEASE CLINIC\*

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(Received for publication, February 20, 1922)

ON July 9, 1918, Congress enacted legislation which established a Division of Venereal Diseases in the United States Public Health Service, created an Interdepartmental Social Hygiene Board, and made appropriations for the activities of the Division and the Board. The appropriation carried in this legislation, to enable the Division of Venereal Diseases to cooperate with state boards of health, was two million dollars for expenditure during the two-year period ending June 30, 1920. The Public Health Service made an agreement with the various state boards of health whereby one-half of the sum allotted to each state was to be expended in the treatment of venereally infected persons. For this purpose nearly five hundred venereal disease clinics are now operating throughout the United States. The personnel, facilities, methods of treatment, and volume of work performed at each of these clinics depends entirely upon local conditions and local needs. A general plan meeting certain minimum requirements has been made effective through the coordination of the work brought about by each clinic being maintained under the joint auspices of the state board of health and the Public Health Service. At each of these clinics the local director is responsible for the detailed management of his particular clinic. It is considered desirable to bring to the attention of other clinic directors the detailed methods of managing a modern venereal disease clinic and in the hope that some useful suggestions may be found by those reading this article, the following data are presented:

### PLAN AND METHOD OF ORGANIZATION

The clinic is conducted under the auspices of the Maryland State Department of Health. It is a day and night clinic, and is divided

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\*Assistant Surgeon General C. C. Pierce, in charge of the Division of Venereal Diseases of the Public Health Service, and a Department Editor of this Journal, has undertaken to secure a series of articles describing the work in various venereal disease clinics affiliated with the Public Health Service. The first of these articles appears in this issue. It was prepared by Dr. A. G. Rytina, Medical Director of the clinic described.

into several divisions: Male Venereal, Female Venereal, Syphilis (Male and Female), Social Service, Clerical, and Statistical. Each main division is separate and distinct, and under the charge of an assistant director. The whole clinic, however, is coordinated under the leadership of the director. The director does no active work in the clinic, but is responsible for clinic appointments and discipline, and shapes the policy of its activities, and on account of his age, experience, and established reputation, makes it easier to secure prestige and influence necessary to get community backing and professional support, and gather about him able, energetic young men. The assistant director has actual charge of the working of his division, and not only he but his associates are picked solely because they have a special interest in the branch and are making it their life's work. For example, the workers in the Male Division are genitourinary specialists; those in the Female Division essentially gynecologists, etc. I believe our plan in this regard is a little different from that pursued in most venereal clinics. Experience teaches us that very few capable young men are willing to specialize entirely in venereology and on this account, we treat in addition to venereal infections other genitourinary conditions. By including the latter, which will not represent perhaps more than 5 per cent of the total, not only better men may be obtained but greater interest is manifested in the workings of the whole clinic. We always have a number of volunteer workers or postgraduate students working in our clinic, and the most attractive feature and the one which brings and holds them is the knowledge that they will see and learn something of cystoscopy, ureter catheterization, endoscopy, etc. Similarly, in the Female Division, we can get the services of good, young gynecologists, who not only make careful pelvic examinations with the idea of locating and treating the gonorrheal infection, but with the feeling that in the course of a year a number of operative conditions will be presented. This view and policy will not be highly commended perhaps by men only interested in the public health aspects of the work, but my feeling is, when the proposition is looked at broadly and practically, that the best results will be achieved, even from the public health standpoint. It is most important that the two clinics, male and female, be separated. We accomplish this by having separate rooms and separate clinic hours: for males (Mon-





Fig. 1. Section of waiting room Venereal Disease Clinic, Mercy Hospital.

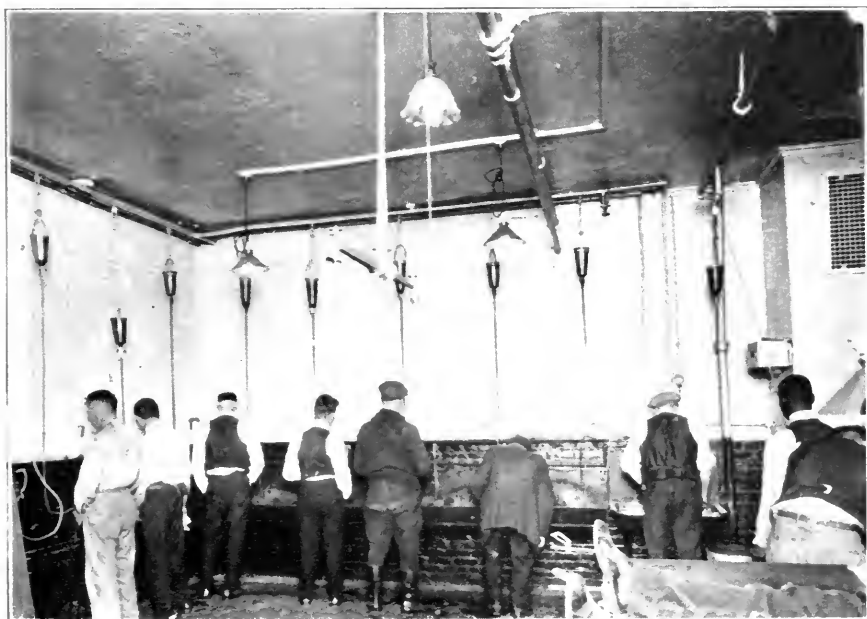


Fig. 2.—Section of treatment room. Irrigators in male venereal department.



day and Thursday 8 to 10 P.M.), and for females (Tuesday and Friday 8 to 10 P.M.). During the day, the hours for males are from 1 to 3 P.M., females (Mondays, Wednesdays, and Fridays 12 to 1 P.M.). An entirely different group of men work in the male and female divisions, but the same team treats both the male and female syphilis patients. The Syphilis Department meets two evenings a week with the male division (Mondays for arsphenamine and Thursdays for mercury injections) and one evening a week with the female division (Fridays—when both arsphenamine and mercury injections are administered as the cases may require). Antiluetic treatment is also administered to both males and females in the day clinic, but in widely separated rooms.

The Director is Professor of Genito-Urinary Surgery at the University of Maryland School of Medicine. Several of the clinic staff are instructors on the teaching staff of the same University. The advantages of the Clinic are open to senior medical students, where all their instruction in venereal diseases is received. The students visit the clinic in groups, and are taught all the essentials, and the proper handling of venereal diseases along modern lines. The medical students, however, are not allowed in the female clinic rooms at any time. The importance of placing our large material at the disposal of medical students for teaching purposes, is not only of advantage to the medical school which gives the clinic every cooperation, but the material used for teaching purposes not only increases interest on the part of the medical student in this important branch, but fits him better for handling these diseases when he engages in practice.

#### METHOD OF HANDLING PATIENTS AND SYSTEM OF RECORDS

A patient presenting himself for the first time in our Clinic, is shown into the Record Room, where the clerk enters his name and address, civil state, age, etc., in a registration book. A sample entry would be as follows:

<i>History No.</i>	<i>Name</i>	<i>Address</i>	<i>Color</i>	<i>Age</i>	<i>Civil State</i>	<i>Numerical Reg. No.</i>
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A history sheet corresponding in number to that assigned in the Registration Book is then made out on the typewriter, and the statistics appearing in the Registration Book are repeated on each individual history, and in addition, the nature of the patient's complaint. An admission card, corresponding in number

to that of the history sheet, with the patient's name written thereon, is then attached to the history sheet, and both are deposited in a special basket for *first time* patients. The patient is then told to go to the Waiting Room until called, and in the meantime, is given several pamphlets to read over. Sample history, admission card, and "follow up" letters are printed at the end of this article.

We have found by experience that the most efficient method of handling patients as a whole is to treat those patients first who have reported previously one or more times. For this purpose, an admission ticket box, with compartments for each individual doctor, is placed on the door leading to the main treatment room, and old patients coming in deposit their tickets in the box of the doctor who has charge of the case.

The doctors at the opening hour of the clinic go to the ticket box and take out the cards of their patients, and call out the names. The patients so called then receive their treatments. When a patient has completed treatment, his card is handed back to him by his doctor, and the patient follows the same procedure on his next visit.

As soon as any doctor has completed treatment of his first batch of old patients, he goes to the basket for *first time* patients, and takes out a history and admission card. The doctor then writes his name both on the history and on the card. The patient is now called in and his card is handed back to him, with instructions as to how to deposit it in the ticket box on his next visit. The doctor then obtains from the patient a thorough genitourinary history, with special attention paid to the complaint for which patient applies for treatment. This is all written out on a separate piece of paper, and enough space is left for the examination notes. This sheet of paper is then attached to the history sheet, and the doctor proceeds with examination of patient. At the conclusion of examination, the doctor hands our stenographer the history and sheet attached, and then dictates the results of examination, which are inserted in shorthand in the space left at the bottom of the sheet.

In the treatment of old patients, each doctor keeps a little memorandum pad on which he jots down the number of patients' cards, with brief notations as to condition, improvement if any, and treatment. When a doctor has finished looking after old patients, he goes to the Record Room, and dictates by number the condition of the patient on that particular day. Each subsequent visit by patient is then recorded in the same manner.

For reference purposes, an index card giving the patient's name, address, history number, diagnosis, and date of first attendance is made out and filed alphabetically. Thus if a patient loses his card, as frequently happens, it is an easy matter to locate his history number by the use of this file record, and issue a new card. Furthermore, an index by diseases is kept, so that we can at any time tell how many patients we have treated for acute gonorrhea, primary syphilis, or any one of the many classifications of infections.

*Syphilis Department.*—A Wassermann test is made of every patient reporting at our clinic. If the test proves positive, or if the *Treponema pallida* has been previously demonstrated, the patient is at once transferred to the Syphilis



Fig. 3.—Section of treatment room.



Fig. 4.—Syphilis department.



Department, and his card is marked with an "L". In this way, patients suffering with syphilis are grouped and their cards deposited in the box of the Director of the Syphilis Division. At frequent intervals, our stenographer goes to the ticket box, and takes out the tickets thus collected. He then goes to the door of the Syphilis Department, and calls out the names of the patients in the order of their time of appearance. He has with him a pad, on which he notes the name and history number of the patient. The card is then handed back to patient, who takes a seat and awaits call for injection of arsphenamine or mercury as the case may be. As each patient receives his injection, inquiry is made by the doctor as to whether patient has had any reaction resulting from previous treatment. Inspection is also made of any lesions, whether or not they have improved or disappeared under treatment, etc. Our stenographer is present in the treatment room, and makes entries on his pad of any reactions, improvements, etc., and these notes are in turn transcribed on the histories.

#### TREATMENT OF PATIENTS

*General Conditions.*—We have a large waiting room for the night patients, which really is the general waiting room of the Mercy Hospital Dispensary. The hospital is located in the busy business and industrial section of the city, centrally located and perhaps the best location in the city for the purpose. In the day clinic hours, two large corridors immediately adjoining the clinic room suffice. If he is a gonorrheal patient he is kept by the physician as long as he is a patient at the clinic. This personal touch and clinging to the patient by the physician is of service to both. It pleases and satisfies the patient more, and makes more skillful the physician. If the gonorrhea is acute, after a careful history and examination of the patient which includes examination of the external genitals, microscopical examination of the smear for gonococci, inspection of the two-glass test, rectal palpation (not massage) of the prostate and seminal vesicles, treatment is prescribed for him. This consists in irrigations by the gravity method, of silver nitrate and permanganate solutions at the clinic and supplying the patient with a bottle of protargol solution (1 to 2 per cent), and an Asepto urethral syringe, two dram capacity, for home use. Our system of irrigating patients can be gleaned from Fig. 1. It consists of a metal trough made of galvanized sheeting, painted black, and with a number of irrigators attached above. By this system, eight patients can be irrigated at one time. After the irrigation, if necessary the patient is placed upon a treatment table, and necessary treatment by sounds, etc., given. If the patient's gonorrhea has become chronic,

regular and systematic massage of the prostate and seminal vesicles is introduced, the passage of sounds at proper intervals carried out, or endoscopic applications made to the posterior urethra, etc. Needless to say frequent examinations are made of smears from urethra, prostatic secretion, etc. Patients are treated until they are cured and not only no longer infectious. Daily notes are made of every patient treated in the clinic.

*Chancroid.*—Our method of treating chancroid is standard and worthy of no special mention. Local applications are made to the sores, of phenol, silver nitrate, calomel or bismuth, or calomel, bismuth and salicylic acid, iodoform, argyrol crystals, mercurochrome solutions, etc. Practically every case of sore is considered specific, until proved otherwise, by dark-field illuminator, Wassermann test, and clinical examination and observation. Every patient who enters the clinic, regardless of his complaint, has a Wassermann made.

*Syphilis.*—If a patient enters the Male Venereal Clinic and is found to be syphilitic, either by dark-field illumination study, Wassermann reaction test or clinical examination, he is transferred with his history and notes to the Syphilis Division. He is again studied and at once put on an intensive antiluetic course of treatment, which consists of arsphenamine and mercury injections (usually 0.4 gm. diarsenol and 1 gr. Hg). A course consists of 8 injections of arsphenamine at weekly intervals, and 15 injections of mercury intramuscularly at seven day intervals. At the end of each course a Wassermann reaction test is made, and if the reaction is negative, further treatment is advised nevertheless, if positive, insisted upon. No patient is considered cured of syphilis until his Wassermann is persistently negative for two years and until he has had a lumbar puncture, and his spinal fluid examination is negative. Our method of giving and of expediting the treatment of syphilis, we think well worthy of mention. It consists of a table 14 feet long and 4½ feet wide, upon the top of which are attached four wooden uprights at regular intervals, these in turn being braced on top by a cross bar. On these uprights are fixed the arsphenamine gravity containers. By means of this inexpensive and yet neat device, four injections of arsphenamine can be given at one time. In a busy clinic, it is very important not to keep patients waiting too long, and by the system of multiple irrigators and the above described arsphenamine outfit, this is accomplished.





Fig. 5.—Women's waiting room.



Fig. 6.—Clinic staff.



*Female Gonorrhea.*—The patients are prepared by nurses or social service workers, and the treatment consists of local applications of tincture of iodine or silver nitrate to the urethra, cervix—inside and out—and the insertion of glycerine tampons. Hot douches of bichloride and antiseptic powders are also prescribed for home treatment.

*Hospital and Detention Facilities. Morrow Hospital.*—Our clinic is most fortunate in having unexcelled facilities for hospitalization and detention of venereal males and females. Members of the Male Venereal Division are also visiting surgeons at the Morrow Hospital, 1122 N. Mount St. This is a 100 bed hospital, devoted exclusively to the treatment of male venereal and genitourinary conditions along the most modern and approved lines. All patients in the Male Venereal Clinic developing complications of gonorrhea, such as epididymitis, arthritis, etc., or whose cases are very virulent, or who are unable to carry out proper home treatment are admitted to the Morrow Hospital. Similarly, virulent and infectious cases of syphilis are sent to the Morrow Hospital until they are no longer a menace to the public health. At the present time there are 26 male patients receiving treatment at the Morrow Hospital for venereal disease infection, who were formerly ambulant patients at the Clinic. As their condition improves, they are discharged from the hospital, with instructions to return to the Clinic and conclude treatment again as ambulant patients. All patients in the Morrow Hospital are under quasi detention. They are allowed off the premises only on a "pass" for good reason and for a short time only. No night passes are issued except for emergency reasons. Police aid is available, but very rarely necessary.

*Female House of Refuge.*—The Female House of Refuge, located at the corner of Hollins and Poppleton Sts., is under the control of the Sisters of The Good Shepherd. These good sisters recognizing the importance of the campaign we are waging against venereal diseases, have placed at our disposal a ward for the isolation, detention, and treatment of venereally infected females. Members of our staff visit regularly this institution and carry on the necessary treatments for both gonorrhea and syphilis. Many of our patients are young and are committed by legal procedure to this institution until they are of age, and not only sufficient time is afforded us,

therefore, in most cases to carry out full and complete treatment, but rehabilitation and vocational methods are carried out by the sisters in most commendable fashion. At the time of the present writing 32 such patients are under care at The House of The Good Shepherd.

*Staff Meetings.*—Once a month a staff meeting is held. Everybody connected with the staff attends, Director, Asst. Director, associates, social service workers, clerks, volunteers, and postgraduates. Attendance by members of the staff at these meetings is obligatory. They are held either at the Morrow Hospital or in the clinic rooms.

1. The meeting first takes up the reading of the minutes of the last meeting.

2. Suggestions are asked by the Director leading to better harmony or greater efficiency of the clinic work.

3. Histories are discussed and criticized.

4. Interesting clinic cases are discussed.

5. Review of literature. Each staff member is assigned a journal, and it is his duty to abstract special articles and discuss same before the conference.

6. Remarks (jacking up) by the Director.

7. Social half hour (lunch and play).

#### SOCIAL SERVICE DEPARTMENT. FOLLOW-UP SYSTEM

In due time every patient is visited in the home in order to ascertain the conditions under which they are living. Inasmuch as it requires a long time to accomplish this, the infectious delinquent cases are visited first, or notified by letter of their failure to come to the Clinic for treatment at the appointed time. For instance, if a patient misses an injection of arsphenamine a letter is sent at once reminding him or her of their failure to come to the Clinic. (Copy of letter is printed below—No. 1.) If this patient fails to appear a second time, a personal visit is made and the patient told of the importance of taking regular treatment, and warned of the dangers resulting if they fail to do so.

In the case of patients who come to the Clinic for an examination, and are found to be infected, but fail to return for treatment, a letter is sent to these patients telling them of their condition, and urging them to return at once to begin treatment. (Sample letter is shown below—No. 2.)

In visiting the homes of unmarried patients, it is necessary for worker to represent herself as an agent of some description in some cases. In other instances where the patient is a young girl, and it is deemed unwise to go direct to the home, a letter is sent requesting her to meet worker at an appointed

place in the neighborhood, then a visit is paid to the home, where a more satisfactory interview can be held.

It is only by studying the disposition of the different patients that worker learns the most effective means of holding the patient's confidence and encouraging their regular attendance at the Clinic.

**U. S. GOVERNMENT CLINIC**  
**N. W. COR. CALVERT AND SARATOGA STREETS**

HIST. NO. 6948  
FOR MEN (ONLY)  
MONDAY AND THURSDAY EVENINGS, 8 TO 9 P. M.

DATE Jan. 9, 1922  
DAILY, 1 TO 2 P. M.

DR. Goldman FOR WOMEN (ONLY)  
TUESDAY AND FRIDAY EVENINGS, 8 TO 9 P. M.

NAME Smith, Samuel

ALWAYS BRING THIS CARD WITH YOU

After the patient has been examined, and found infected, he or she is sent to worker for a first interview by the doctor. This interview is made as brief as possible. If the man is married, he is questioned as to the health of his

Mon.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
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Dec.																															

(Sample Follow Up Card No. 3)

wife and children, and it is suggested that it might be advisable for him to have the wife come to the Clinic for an examination, or if he prefers worker offers to visit the wife and talk with her.

In the cases of single girls where an operation is necessary, and they are living with their parents, the mother is seen and told that the girl had been attending the dispensary, where she was treated for "female trouble", but that an operation has been advised by the doctor as the only permanent cure. Little or no trouble is experienced with the family in making arrangements for her admission to the hospital.

All infectious cases who refuse to take treatment or fail to do so are reported to the Department of Health, and they send a Health Warden to such persons, notifying them that they are obliged to take treatment under the Health Regulation Act not only for their own sake, but for the protection of the community at large.

The date of visit paid to the patient is entered in worker's memorandum book with result of visit, and this is afterwards entered on the history.

In order to check up the patient's visits to the clinic a card system is used (sample of which is given—No. 3). This method is very simple, the date of visit is checked in the space for that purpose and the kind of treatment given. The card is then filed under the date when he is told to return, and in the event of failure to do so, a letter is sent at once. If he does not respond on the next date a personal visit is made to find out the cause of absence.

#### STATISTICAL DEPARTMENT

For statistical purpose and in order to complete information necessary for the monthly clinic report for the United States Public Health Service, a clerk is employed to tabulate the necessary information. After notations of the return of patient to the clinic, his condition, progress, and treatment rendered are made on the history sheet, they are then given to the tabulating clerk who notes the necessary statistical data. At the end of the month these figures are totaled and transferred to the regular monthly clinic report.

The accounting for the clinic is done in the offices of the State Department of Health. Requisitions for materials are submitted to the Chief of the Bureau of Works, Accounts, and Property of the State Department of Health, who after approval of the requisitions, procures the necessary supplies. Payrolls are also prepared by him and monthly salary checks distributed.

Clinicians who are on duty two hours daily and two evenings per week receive \$75.00. Clinicians who are on duty two evenings per week only, receive \$50.00 per month. The social service worker receives \$125.00 a month; a stenographer, \$100 per month; and a clerk \$25.00 a month, for part time service.

Fees paid by patients for drugs are remitted weekly to the State Department of Health and are placed to the credit of the clinic account.

The expenses of the clinic are all kept in the Accounting Department of the Department of Health, and all invoices for materials paid by that office.

STAFF

John H. Fulton, Secretary, Maryland State Department of Health.  
R. H. Riley, Chief, Bureau of Communicable Diseases, Maryland State Dept.  
of Health.

A. G. Rytina, Director.

H. Goldman, Asst. Director, Male Division.

E. P. Smith, Asst. Director, Female Division.

H. T. Collenberg, Asst. Director, Syphilis Division.

A. J. Gillis, L. K. Fargo, E. L. Briscoe, J. F. Hogan, O. Costa, D. J. Pessagno,  
E. L. Foley, L. C. Roberts, F. L. Benz, H. L. Tolson, I. P. Robinson, Male  
Clinic Associates.

F. L. Benz, L. C. Roberts, Female Clinic Associates.

Miss Nan Gorsuch, Head Social Service Department, Mrs. B. B. Darby, Asst.  
Social Service Department.

Walter N. Kirkman, Chief, Accounts and Property. J. Davis Donovan, Law  
Enforcement Officer.

E. V. White, and W. F. Gillis, Stenographer and Clerk. Richard Benburg,  
Messenger.

The volume of work accomplished at the clinic described above during the  
calendar year 1921 is shown in the following data:

Total number of treatments (old patients) .....	20,193
Number of new patients treated .....	1,734

Total .....	21,927
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Form No. 1.

MARYLAND STATE BOARD OF HEALTH  
MERCY HOSPITAL CLINIC  
SARATOGA AND CALVERT STREETS, BALTO., MD.

Mr. .... Jan. ....  
.....

DEAR SIR:

Our records show that you were not cured at your last visit and you are  
requested to return to the Mercy Hospital at your earliest convenience.  
If it is not possible for you to do so, kindly notify us by mail, giving the reason  
for your absence.

Clinic hours are 1 to 2:30 P. M. daily and 8 to 9 P. M. Mondays and Thursdays.

Yours very truly,

A. G. RYTINA, M.D., Director.

Form No. 2.

MARYLAND STATE BOARD OF HEALTH  
MERCY HOSPITAL CLINIC  
SARATOGA AND CALVERT STREETS, BALTO., MD.

Mr. ....

Jan. ....

DEAR SIR:

Our records of your examination show that you need treatment for your malady. You are therefore, requested to return to this clinic at your earliest convenience. If it is not possible for you to do so, kindly notify me by mail, giving your reasons.

Clinic hours are 1 to 2:30 P. M. daily and 8 to 9 P. M. Mondays and Thursdays.

Yours very truly,

A. G. RYTINA, M.D., Director.

NAME Smith, Samuel	W. C.
ADDRESS 1620 E. Pratt St.	W
DIAGNOSIS Chancroid.	No. 6948.
ADMITTED Jan. 9, 1922.	
DISCHARGED 2/27/22.	

(Sample Index Card)



Form C. D. 105

Dr. Goldman.

No. 6948.

MARYLAND STATE DEPARTMENT OF HEALTH  
DIVISION OF VENEREAL DISEASE CONTROL

HISTORY SHEET

NAME	Smith, Samuel	DATE	Jan. 9, 1922.
ADDRESS	1620 E. Pratt St.	OCCUPATION	laborer
RACE	w	SEX	m
		CIVIL STATE	single
		AGE	26
SOURCE OF INFECTION.....	BY WHOM REFERRED		poster
PRIMARY DIAGNOSIS	Chancroid.		
COMPLAINT	Sore on penis.		

HISTORY: (Should include chief complaint, family history, previous personal history, present illness, physical examination and laboratory findings)

F. H. Negative to TB, Cancer, or Syphilis.

P. H. Measles and mumps in childhood. No operations, Had gonorrhea 4 years ago, treated with internal medicine for 6 or 7 weeks, and recovered without complications. Denies syphilis.

P. C. Began 10 days ago with appearance of small pimple on penis. This has gradually increased in size. Incubation 5 days. Previous exposure 2 weeks. Has used no treatment and consults clinic for same.

EXAM. External genitals normal, with the exception of small ulcer on left side of shaft of penis, about the size of a pea. Sore shows no induration. No urethral discharge. Gland 2 clear, shreds. No glandular enlargement. Rectal examination shows normal prostate and seminal vesicles. Dark-field examination of smear from ulcer negative to spirochetes. Blood taken for Wassermann: Negative. RxPhenol applied to sore.

1/12/22. Sore looks better. Rx—Phenol continued.

(Sample History Sheet)

## INTRASPINAL THERAPY IN NEUROSYPHILIS

BY J. A. FORDYCE, M.D., NEW YORK

(Received for publication, February 6, 1922)

IN A paper by Dercum on "The Functions of the Cerebrospinal Fluid" (Archives for Neurology and Psychiatry, Vol. iii, p. 230, 1920) the employment of subarachnoid therapy is condemned for the reason as stated by the author, that substances introduced into the fluid rapidly disappear, passing through the arachnoid villi into the venous system of the dura and also to a lesser extent through the lymph sheaths of the cranial and spinal nerves without entering the parenchyma of the central nervous system in the slightest degree. He further says the mistaken view that the nutrition of the nervous system is carried on by means of the cerebrospinal fluid has led to attempts to utilize the cerebrospinal fluid of the subarachnoid space as a medium of medication. His arguments against the method appear to be based chiefly on its use in two intractable affections of the central nervous system, namely paresis and tabes. He does not refer to other types of neurosyphilis, or to the conditions which antedate by years the fully developed types of parenchymatous encephalitis and tabes. He furthermore states that the benefit which may follow the procedure in question is due entirely to the incidental drainage and hyperemia and not to the drug content of the serum introduced. The use of the subarachnoid injections was not begun by Swift and Ellis under the mistaken idea that the nervous system received its nutrition from the spinal fluid but because the subarachnoid space had been successfully employed in the treatment of epidemic cerebrospinal meningitis. It was also clearly proved by them that the salvarsanized serum had definite and marked spirocheticidal properties.

Many types of neurosyphilis have their site and origin in the spinal or cerebral meninges with their blood vessels and are limited to these structures. Meningovascularitis simulates closely paresis and cannot always be differentiated clinically from it. In true paresis there is in the majority of cases a coincident meningitis

which at times occupies the foreground and overshadows the deeper encephalitis. In the greater number of active cases we clinically call tabes, the spinal fluid findings are those of an accompanying meningitis. It was not alone, therefore, from theoretical considerations of the functions or physiology of the cerebrospinal fluid that the method of treatment was originated and employed by Swift and Ellis, but also from the knowledge acquired by the use of the antimeningitis serum and from a recognition of the pathologic condition in all types of syphilis of the central nervous system. Failure of the older therapeutic method to benefit or cure not only tabes and paresis but the majority of cases of so-called cerebrospinal syphilis was an additional reason for the effort to reach more directly the pathologic process.

It is admitted by all who employ intraspinal therapy that the earlier and more pronounced the meningitis the more rapidly is the cure effected. If, as stated by Dercum, the spinal fluid finds its exit through the venous channels of the dura and the lymph channels of the cranial and spinal nerves, may we not here have a partial explanation of the action of the medicated serum on the structures with which it comes in contact? During the past eight years my colleagues and I have used the method in a large number of cases of all types of neurosyphilis, many of which have been treated to the limit with mercury and salvarsan intravenously and others by spinal drainage combined with intravenous salvarsan. The number of cases treated with careful and prolonged laboratory control of the blood and spinal fluid has enabled me to make a comparison of the results obtained with those achieved by the advocates of the intravenous method together with or without drainage of the fluid.

Numerous cases have been entirely cured and many greatly benefited after the failure of the methods so strongly advocated by Dercum and Sachs. If the results of observation are of any avail a careful study of such cases should convince any observer with an open mind that results have been achieved that could not have been by any other procedure. In numerous cases of optic atrophy the process has been permanently arrested by intraspinal medication after the failure by prolonged intravenous treatment. These results have been fully confirmed by the careful control of experienced ophthalmologists. May not the exit of the medicated

fluid through the lymph channels of the optic nerves and the control of the accompanying meningitis afford a logical explanation of these results? The cures obtained in types of syphilis of the central nervous system by intraspinal therapy after repeated failure by intravenous treatment with or without coincident drainage appeal to me as more convincing arguments in its favor than theoretical reasons why such results are not possible or are due to incidental factors. It might further be added that if the use of salvarsanized serum is unscientific and valueless in syphilitic meningitis, the use of antimeningitis serum is equally unscientific and valueless in infectious cerebrospinal meningitis. It would be more scientific for Dercum to say that parenchymatous syphilis when fully developed is beyond the reach of any known therapeutic procedure and that our endeavors should be directed to early recognition and treatment of the conditions which antedate the degenerative stage. The problem of the future in neurosyphilis is one of prophylaxis. This can only be made real and solved by prolonged study of the infection in all its stages and especially of the spinal fluid in the first year of the disease. It is then that we may detect and anticipate by treatment incurable degenerations.

In treating a large number of patients with neurosyphilis we encounter types which present all the clinical signs and symptoms of paresis and often also with its cytobiological formula. Some of these cases are cured by prolonged intraspinal treatment. The response to treatment of such patients leads us to the conclusion that we have to do with types of superficial encephalitis combined with meningitis and blood vessel involvement rather than with deep-seated encephalitis. It is not always possible, therefore, to predict with certainty the outcome in cases of this type.

As a result of experience I have long since ceased to drain the fluid preliminary to the introduction of the serum. The latter is introduced under pressure and more fluid is present in the subarachnoid space than normal. My clinical and serologic results have been vastly better since the incidental drainage has been discontinued. Granted that the cerebrospinal fluid is equivalent to a normal salt solution and chiefly concerned in the hydraulic suspension of the brain and cord, it must also be conceded that in neurosyphilis it is something more than a fluid containing sodium chloride. In some manner the products of syphilis have gained

access to it. It contains lymphocytes, excess of globulin and the Wassermann producing substances. By osmosis, or diffusion, or in some other way these pathologic products have changed the fluid from a simple salt solution to one which as a rule accurately reflects the activity of the syphilitic disease. If the products of syphilis can find their way to the fluid it is safe to assert that the specific remedies can in a similar manner gain access to the disease-producing organisms. At any rate this theory conforms with the clinical results and serves as well as any other explanation.

It is well known to one who correlates his clinical work with laboratory control that syphilis of the nervous system may exist without coincident clinical or serologic evidence of infection of the general blood stream. In certain of these cases there is no interchange of the products of syphilis in the nervous system with the blood, neither is there any penetration of drugs introduced into the blood stream to the central nervous system. These statements have been confirmed time and again and admit of no denial. It is in such cases that remedies applied through the ordinary channels are of no avail. On the contrary remedies used by the intraspinal route benefit or cure patients who can be influenced in no other manner. If we admit that the arsenic introduced into the subarachnoid space rapidly disappears it is also true that the same drug is also rapidly eliminated when used intravenously. The rapid or slow elimination of a specific remedy has little relation to its therapeutic effect. The chemoreceptors of the organisms attract and attach themselves to the parasitropic remedy, even though greatly diluted by the blood stream or the cerebrospinal fluid. A minute quantity of morphine or strychnine is also greatly diluted by the blood, but attracted to the living cells of the central nervous system. Arguments as to the inertness of specific drugs when diluted in this manner fail to take cognizance of the special affinities they possess and their changed chemical relations when in contact with the tissues.

It is a simple matter to deny on paper the value of a certain therapeutic procedure and to fabricate a premise from which apparently logical deductions are drawn. If the deductions agree with the facts well and good. If directly opposed to them we must assume the premises are wrong and the superstructure built on them falls. Theoretically curative results may be impossible to

obtain by the method under discussion when worked out in the physician's library but they are real to the living and suffering patient when properly employed.

Intraspinal treatment cures certain types of neurosyphilis in which intravenous treatment alone or when combined with spinal drainage has failed. This statement is based on many years of experience in which clinical cures have been carefully controlled by laboratory tests and by several years of close observation in which no relapse took place. One is therefore justified in drawing the logical conclusion that the method is of value in spite of the statement made by Dereum that it is unscientific and opposed to theoretical physiologic laws governing the circulation of the cerebrospinal fluid. Spinal drainage as endorsed by this author is of some value and may in certain cases facilitate the entrance of salvarsan given intravenously. It more often fails to do more than reduce the cell count. It has little or no effect on the Wassermann reaction or the globulin content. It cannot be endured for a sufficiently long time in chronic types of neurosyphilis to effect a cure. These cases require months or years of treatment. It is practically impossible to continue drainage in the manner outlined by Dereum for that length of time.

The value of therapeutic procedures in neurosyphilis should be appraised by the permanence of the results not only on the clinical signs and symptoms but also on the changes in the cytobiology of the spinal fluid and blood. If patients are not kept under observation for several years and controlled in this manner statements made by clinicians as to the effect of this or that method of treatment have little or no significance. I have fortunately been able to control by laboratory and clinical observation a large number of patients from one to four years after intraspinal treatment and found all the phases in the fluid negative with arrest of the pathologic process. In these patients all other methods of treatment had been previously employed without effect on the fluid findings and with little influence on the clinical picture. The advocates of intraspinal therapy have endeavored to recognize its limitations and to use it only when other methods failed and when the *fluid formula offered clear indications for its employment*. The method is enduring the test of time in the hands of clinicians who are

familiar with its technic and who are trained in interpreting the findings of the laboratory.

In certain types of curable syphilis of the central nervous system the positive phases persist for years and require prolonged treatment. Rapid results are only to be anticipated in early cases of meningitis and in the more superficial forms of late neurosyphilis. The toxic effect of our drugs as well as possible harmful results from prolonged drainage or intraspinal injections should always be kept in mind. Many patients become intolerant to the prolonged use of arsenic and must either cease treatment by it altogether or recourse be had to some alternative. When there is intolerance to intravenous salvarsan the serum of another treated case may at times be advantageously employed in syphilis of the central nervous system.

An endeavor should be made to consider all sides of the therapeutic problem in neurosyphilis rather than to support a favorite and untenable theory.

## PRACTICAL OBSERVATIONS ON SYPHILIS. II

BY H. H. HAZEN, M.D., WASHINGTON, D. C.

(Received for publication, March 13, 1922.)

### Section 6

#### CUTANEOUS COMPLICATIONS

THE cutaneous complications of syphilis may be divided into dyschromias, atrophies, scars and keloids as the direct results of the pathologic processes in the skin. Subcutaneous calcification may occur deeper in the corium. As the result of irritating discharges we may see varying degrees of dermatitis or venereal warts. Telangiectases may develop in association with the infection. Keratoses appear at times. Cancer may appear in the scar tissue. Arteritis may produce secondary skin changes. Eczema may occur also in connection with syphilis. And lastly some sarcoids and even erythema nodosum and scleroderma have been attributed to this infection. In addition urticaria is occasionally due directly to syphilis.

### Section 7

#### LESIONS OF THE NAILS AND HAIR

Lesions of the nails and hair are infrequent in syphilis. They might be divided into three different types, first, lesions of the nail proper, second, changes in the nail bed, and third, a syphilitic paronychia.

1. There may be a brittle condition of the nails, so that the free ends tend to split and break, and as a result the nail border is splintered or serrated. All of the nails may be involved but more especially those of the hand. There is probably no thickening of the nail, but simply a change in its quality so that it is more brittle.

2. In the dorsal surface of the nail there may be pits, sometimes arranged in a line from the root forwards. Batut states that they begin as whitish points which can be dug out, and which leave roughened, black holes.



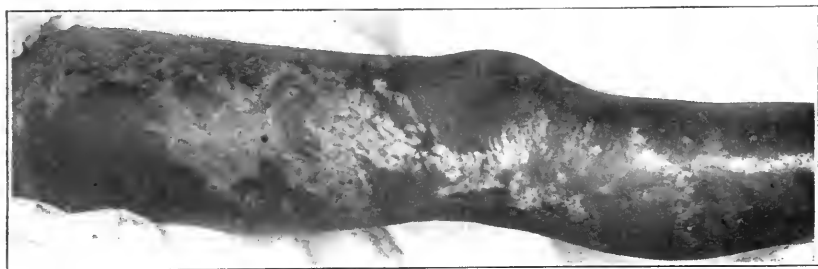


Fig. 29.—As a result of syphilis remarkable pigmentary changes may develop. These lesions are not always influenced rapidly by treatment.



Fig. 30.—Symmetrical saucered nails of syphilis. (Collection of Dr. H. R. Varney.)



Fig. 31.—Syphilitic alopecia usually has a "moth-eaten" appearance. (Collection of Dr. Richard L. Sutton.)

3. The whole nail may become dull, dry, thick, brittle and hence cracked at its free margin. Casanave states that in some instances there is a distinct line of demarcation between the diseased and sound parts. This is due to the fact that a diseased portion grows up behind the sound section, or that a healthy nail is again making its appearance behind the syphilitic portion.

4. Rarely there occurs a hard, wedge-shaped thickening of the distal end of the nail.

5. The nail may exfoliate without any subjective or objective symptoms.

6. Heller has recently published two cases which are sufficiently described by the title that he has given them, namely, "*Striæ longitudinales medianae unguium syphiliticæ.*"

7. It is well known that any disturbance of nutrition may cause a grooving of the nails. Whitfield has noted that this occurs in syphilis as well as in other diseases.

8. Vorner has described black pigmented spots in the lunula, developing at the same time as a generalized secondary eruption.

9. Dr. H. R. Varney considers that "spoon nails," whose general characters are well shown in the illustrations, are pathognomonic of syphilis. These changes are rare, as I have looked for them for two years and have not seen a case.

The second type of syphilitic nail is that in which the nail changes are secondary to local inflammatory changes in the surrounding tissues. Of this there are two types, where there is a papule or pustule on the nail-bed, and where there are syphilitic lesions surrounding the nail. Both of these eruptions are said to be more common than the type above described.

Heller calls the first "the isolated papule of the nail-bed." It may occur at any time during the exanthem. A small discoloration first appears under the nail, this becomes red and then yellow, and the overlying part of the nail gets thin and then finally crumbles away, thus leaving a hole. It is practically always limited to one finger.

The last type of lesion is called paronychia, perionychia, paronychia desquamativa and syphilis ulcerosa unguium. Several nails or but one may be affected, and the thumb is the favorite site, possibly because more exposed to injury. On the foot the great toe is the

usual location. The first symptom is swelling and redness of the tissues around the nail, usually with some pain. The inflammation may extend beneath the nail to the matrix and nail-bed. Either a crusted area or a deep ulcer may result, and the nail may be lost, sometimes permanently.

#### SYPHILITIC ALOPECIA

Klotz has written an excellent article upon syphilitic alopecia. He calls attention to the fact that alopecia in syphilis is not as common as many of the textbooks would have us believe. We should always remember that every individual normally sheds his hair and that a slight daily loss is a perfectly natural and physiologic phenomena. However, in something under 10 per cent of all cases of early syphilis there is a characteristic loss of the hair in patches especially upon the back of the head. All of the hair in these spots does not fall, but from one-fourth to nine-tenths of it does drop. The size of the individual patch varies from one-half to two inches in diameter, and several patches may fuse. The general appearance has been described as "moth eaten," "mangy," "as if the hair had been carelessly cut with a dull pair of scissors," and as "alopecia in clearings."

It is generally believed that the toxins of the treponemata are responsible for this fall. In exceptional cases as White brought out in the discussion of Klotz's paper complete and permanent baldness may result. The type of the disease is most common upon the scalp but may extend to the eyebrows, and even to the axillae and genital regions. It is also probable that in severe cases of syphilis there may be a general nonlocalized loss of the hair of the scalp just as occurs in association with other diseases, and lastly there may be a syphilitic exanthem upon the scalp, and the hair fall at the site of the syphilides.

### Section 8

#### AFFECTIONS OF THE MOUTH AND THROAT

In connection with the subject of syphilitic diseases of the mouth attention should be called to the excellent atlas of Zinsser's which portrays both the syphilitic lesions and those diseases which may stimulate them.



Fig. 32.—Mucous patches are the typical mucous membrane lesions.



Fig. 33.—Perforation of the palate is almost pathognomonic of syphilis. (Collection of Drs. Fordyce and MacKee.)



Fig. 34.—Interstitial gummatous glossitis is fairly common and gives rise to deep fissures.



Fig. 35.—Gummata of the tongue may be solitary and may resemble cancer. (Collection of Dr. Richard L. Sutton.)

The secondary lesions are a part of the superficial widespread involvement that is the result of the septicemia that forms the pathologic basis for the early stage. At the same time it should always be remembered that the mucous membrane manifestations are prone to linger longer than are the cutaneous lesions and that they are often more resistant to mercurial treatment.

At the time of the appearance of the generalized eruption there may appear upon the mucous membranes simple erythematous spots, which may be either large or small and either transient or of long duration. These lesions give rise to no subjective disturbances and are frequently overlooked.

The most frequent and characteristic type of syphilis of the mouth is the mucous patch, sometimes called the erosive syphilide. This is round or more frequently oval, and practically never over two centimeters in diameter, and simply represents a syphilitic papule that has become transformed by its environment of heat, moisture and pressure. These mucous patches are most common on the inner surfaces of the lips, especially at the angles of the mouth, but are also found upon the pillars of the fauces, the tonsils, the tongue, the buccal mucosa and even upon the pharynx. The surface of these patches is usually a gray shining membrane that, when detached, reveals a superficial ulcer beneath. The lesions are sharply circumscribed and there is usually no inflammatory areola surrounding them.

They may become raised and hypertrophied due to the epithelium increasing in thickness, and then appear as rough, granular, even almost frambesiform lesions that often arise abruptly from normal mucous surfaces; they may be surrounded by a considerable areola of inflammation.

In addition to the lesions already described, true papules may appear upon the dorsal surface of the tongue and macular or annular lesions upon the lips. An interesting type of lesions is the large annular lesion of the roof of the mouth.

In the course of malignant syphilis severe ulcerations of the mouth and throat are usually found at an early date.

The diagnosis of secondary syphilis of the mouth is not always an easy matter, for there are a number of conditions that must be ruled out. It is well to point out that the mouth swarms with treponemata of various kinds, hence too much stress should not be

placed upon examination with the darkfield illuminator. The presence of a positive Wassermann reaction is, of course, of great value, always remembering that a patient with an old history of syphilis may very well have some other condition as well. The following conditions must be differentiated:

Patches of any kind that have been touched with silver nitrate may markedly resemble mucous patches. Ulcers or scar tissue may follow the biting of the tongue, lips, or buccal mucosa.

The clinical manifestations of mercurial stomatitis are usually very characteristic, but inasmuch as mercury is usually taken by syphilitic patients, and inasmuch as mercury may cause papules and ulcerations, the diagnosis at times may puzzle the wisest of us. As a general rule typical mercurial stomatitis with its diffuse redness and swelling of the mucous membranes, salivation, the pus covered ulcerations upon the gums, swollen tongue, ulcers upon the cheeks produced by the teeth, and the marked fetid odor present a picture which is easy to recognize.

Just as there are drug eruptions upon the skin, so may there be within the mouth. The use of potassium iodide, phenacetin, antipyrin and other coal tar derivatives produces eruptions in the mouth that may at times simulate syphilis.

The lesions of lichen planus upon the oral mucosa may simulate a syphilitic eruption, but the finding of the characteristic eruption upon the other portions of the body will enable the physician to make the correct diagnosis.

Erythema multiforme at times produces a superficial ulceration, especially upon the tip of the tongue and lips; the diagnosis is best made by lesions upon other portions of the body.

The lesions of aphthous stomatitis are especially apt to be mistaken for mucous patches. In most cases it is not difficult to make a proper differential diagnosis, for the lesions of aphthous stomatitis appear suddenly, either singly or in groups, are painful, and are surrounded by a marked inflammatory areola. At first the central portion of the lesion is covered by a yellowish exudate that later turns gray. These lesions rarely last more than four or five days.

The transitory benign plaques of the tongue should not cause any trouble, inasmuch as they vary much in size and shape from day

to day, a thing that a secondary syphilitic eruption never does. If seen but once, they may resemble annular syphilides, but the history should then save the day.

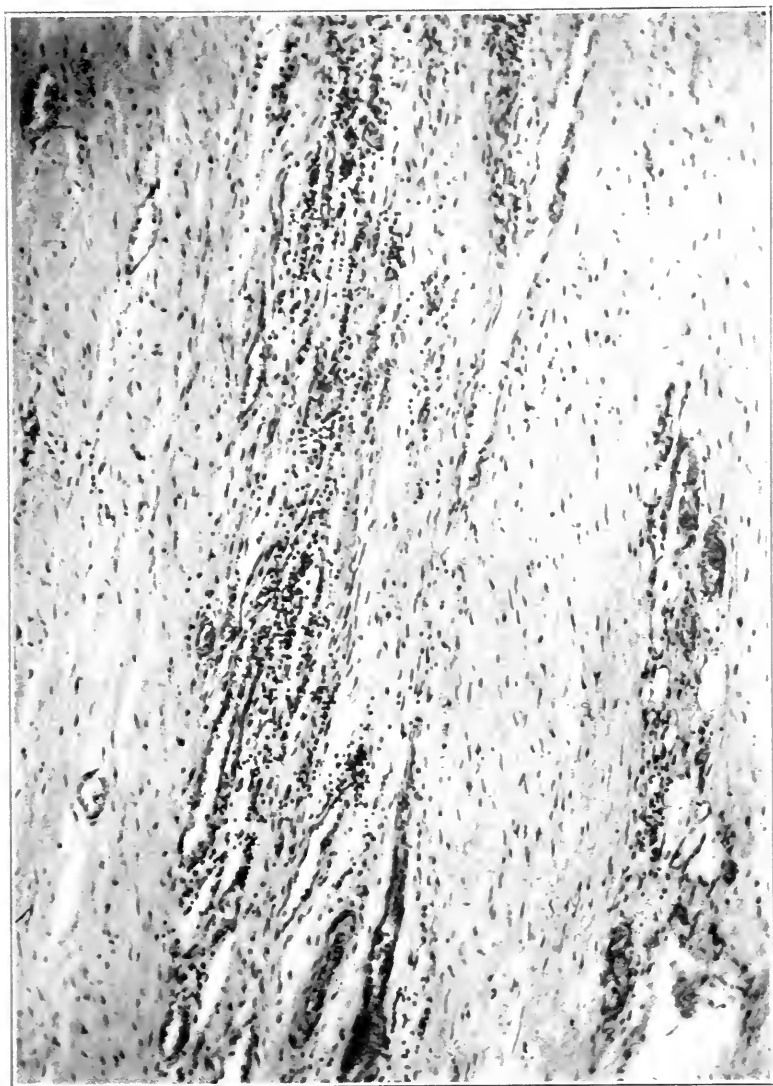


Fig. 36.—Early stage of aortitis, showing characteristic lymphocytic and plasma-cell infiltration about the small vessels in the adventitia. (Collection of Dr. John A. Fordyce.)

## LATE LESIONS

Syphilitic lesions of the mouth and throat during the late stage of syphilis are very common, and may assume many forms. The lips, tongue, hard and soft palate, the tonsils, the pharynx, in fact any structure within the mouth can be attacked. The tertiary le-



Fig. 37.—Later stage of aortitis, showing advanced sclerosis of the vessel walls.  
(Collection of Dr. John A. Fordyce.)



sions are usually characterized by the destruction of tissue due to gummous growths. All are analogous to the growths in the skin and other organs. Small or large nodules may develop upon any



Fig. 38.—Even small aneurysms cast a definite shadow. This is one of the descending arch.

portion of the oral mucosa; these may either break down to form more or less superficial ulcers, or may become sclerosed and form flat, reticulated cicatrices. More often, however, the gummata commence in the submucous tissues and as a result ulcers develop. In general the syphilitic neoplasms of the mouth have no special tendency to spread, yet those of the lips, tongue and particularly those of the soft palate and fauces, may become large tumors, which upon breaking down cause very large ulcers. When this occurs the ulcers have irregular or arched borders, and often undermine the mucous membranes. The floor of the ulcer is uneven and bleeds easily, and is covered with either pus or a serous exudate. As a rule syphilitic lesions do not cause any great amount of pain. These ulcers are especially common about the soft palate and fauces, and frequently cause very extensive destruction of tissue within a short time. It is not uncommon to see the uvula and a large portion of the soft palate totally gone. Associated with such lesions there is always a marked erythema of much of the oral mucosa. Similar lesions upon the walls of the pharynx may occur, either independently or in connection with syphilitic lesions in other parts of the mouth. At times death may ensue from the rupture of a large blood vessel.

The gummous processes in the lips and tongue usually do not run so violent a course, for the tissues are denser and more resistant, so the lesions are usually smaller and more sharply circumscribed, and resemble those found upon the skin to a more marked degree.

It is not rare for gummata to originate from the underlying bone or periosteum. This is most apt to occur in the hard palate, and always results in the local necrosis of bone, with the frequent formation of a fistula through the roof of the mouth. At this point it is well to call attention to the great diagnostic importance of such perforations of either the hard or soft palates, for a fistula in either is practically pathognomic of syphilis. It is usual for such a lesion to make considerable headway before the patient is aware that there is any trouble whatever, and frequently the first indication is the sloughing out of pieces of bone. However, the first evidence is, of course, a soft swelling of the mucous membrane over the affected area, the center of which soon breaks down. Very extensive destruction may take place unless treatment is energetically carried out; the mouth and nasal cavity may become one. In all cases of

ulcers of the mouth a probe should be used to determine whether there be any underlying necrosed bone.

The healing of gummous ulcers in soft tissue always results in



Fig. 39.—While gummata of the lymph nodes are rare in the white race, they are much more frequent in the colored. In this instance the submammary node was affected. (Collection of Dr. Caspar Gilchrist.)



Fig. 41.—This shows another view of the same hand shown in Fig. 40.

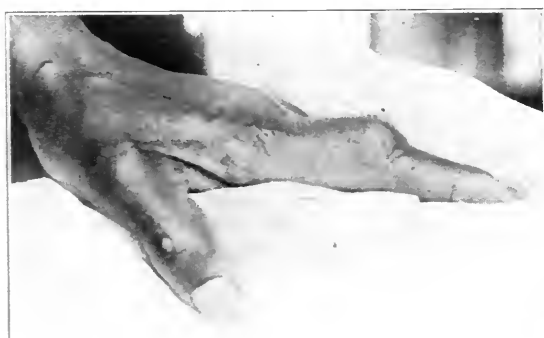


Fig. 40.—Dactylitis may occur in acquired syphilis.

sear tissue formation, and this is apt to be in the form of radiating cicatrices, which distort the noninvolved adjacent tissues. Juxtaim-

posed ulcerating surfaces often become united; hence it is not uncommon to find the uvula and even more of the soft palate united to the posterior wall, while respiration may be carried on through a perforation of the palate. Very small perforations of either the hard or soft palate may close spontaneously, but the large ones remain open unless operated upon.

In addition to the nodular and gummous lesions there is still a third type of lesion, the sclerotic one, that to some extent resembles the diffuse gummata of the skin and the interstitial scleroses that occur in the viscera. This occasionally affects the lips, which become thickened, infiltrated and fibrous, and which may be covered by superficial ulcerations. They usually have a more or less snout-like appearance and are sometimes called syphilitic leontiasis.

Smooth atrophy of the base of the tongue is of considerable diagnostic importance in late syphilis. The base of the tongue is pale, flattened, comparatively smooth and firm but not normal and the lymphoid follicles are few and smooth. This condition is due to a replacement fibrosis. Induration is always characteristic.

#### LEUKOPLAKIA

The question is still undecided as to whether or not leukoplakia is always of syphilitic origin. At the present time fewer observers believe that the majority of cases of leukoplakia are directly due to syphilis. Excessive smoking is undoubtedly a factor in the development of this disease. Another factor that should never be disregarded is irritation produced by rough teeth. McDonagh goes so far as to say that leukoplakia is simply the effort on the part of the tongue to produce a covering that will resist irritation, and that it can usually be cured by removing the irritating cause. However, I have seen a number of instances where this did not suffice to remove the lesions characteristic of the disorder.

The parts usually attacked are the dorsal and lateral surfaces of the tongue and the buccal mucosa at the tooth line. White, thickened plaques that soon become confluent can be seen when well developed. Later there is some fissuring. The tongue is very sensitive to tobacco smoke or to hot or cold food or drinks. A large percentage of these lesions eventually become carcinomatous. Histologically there is both parakeratosis and acanthosis, with an atrophy of

the papillae. There is round-celled infiltration in the submucous tissue.

If the disease is seen early all irritating substances should be prohibited; this means that smoking must be forbidden, and that no highly spiced foods are to be eaten. Neither should very hot nor very cold substances be taken. The teeth should be carefully gone over. If after three months of such a regime there is not recovery, the patches should be removed with the cautery. Under no circumstances should superficial caustics be applied; they are simply irritants and do more harm than good.

## Section 9

### AFFECTIONS OF THE RESPIRATORY TRACT

An idea as to the frequency of syphilis of the respiratory tract may be obtained from the autopsy figures of Symmers. In 314 cases of late syphilis he found lesions of these organs in thirty-five, 10.5 per cent. The larynx was involved twelve times, the lungs twelve times, the pleura twice, the trachea four times, and the nose in five cases.

#### SYPHILIS OF THE NOSE

Chancres of the nose are distinctly uncommon; they usually occur in the vascular areas, and are due to picking of the nose. The lesion has the usual characteristics of a chancre but is rarely diagnosed before the secondaries appear.

Early syphilis of the nose is stated to be common in the congenital type of syphilis, but to be rare in the acquired type. However, Lieven has described both an erythema and papules. When these occur upon the nasal mucosa they give rise to symptoms suggestive of a coryza, and upon examination the turbinates will usually be found congested. Mucous patches have been described as occurring on the anterior end of the septum and upon the inferior turbinate.

Late syphilis of the nose is not especially uncommon: Willijk states that it occurs in 2.8 per cent of syphilitics coming to autopsy. The lesions occur in the same time that other late lesions become manifest. Gummata may start in either the submucous tissue or in the periosteum or perichondrium. The bony septum is a frequent site, but any portion may be attacked. The course is very similar

to that described in the section dealing with gummata of the mouth. If the lesions start in the bone there is rapid destruction of this substance, and there may be great resultant deformity, for the bridge



Fig. 42.—In the same case shown in the two preceding figures the phalanges show considerable destruction of bone. (Roentgenogram by Dr. Walter Van Sweringen.)

of the nose not infrequently becomes depressed to a great degree, due to the lack of a bony support. Frequently there is considerable pain, that may be referred to the head. Tenderness over the bridge of the nose on pressure is stated to be a valuable diagnostic sign. If the gumma is seen before it has ulcerated, it will appear as a firm red swelling that does not shrink upon the application of cocaine. As a matter of fact, it is unusual to see a ease before ulceration has occurred, and then an ulcer is evident, often with some



Fig. 43.—In late syphilis there may be complete destruction of the head of a bone so as to give a picture resembling Charcot's joint. Notice the periostitis of the radius. (Roentgenogram by Dr. Walter Van Sweringen.)

dead bone in it. In some instances the gumma perforate externally and then a sinus will be formed from the nasal cavity to the exterior of the skin. There is usually a very foul odor associated with extensive ulcerations of the nose.

As a result of syphilitic disease an atrophic rhinitis (syphilitic ozena) may result. Owing to the destruction of ciliated epithelium and erectile tissue, the dry surfaces become coated with crusts. Tertiary syphilis must be differentiated from cancer, and this usu-

ally is not difficult, for a cancerous growth is practically always of slower development.

#### SYPHILIS OF THE LARYNX

Secondary syphilis of the larynx is not rare. All clinicians know that it is not uncommon to have a patient with secondary syphilitic lesions show a marked huskiness of the voice upon speaking, a huskiness that has every evidence of being laryngeal in origin. The secondary lesion may be a purely catarrhal one, in which there are macules upon the mucous membranes, although at times there may be an associated edema. Papules have also been described, and occasionally condylomata, the latter usually being situated upon the edges of the vocal cords. In the late stages condylomata may be found, as reported by Aronson; there may be a diffuse gummous infiltration, a nodular lesion, or even a true ulcerating gumma. Lastly there is a perichondritis that usually starts in the arytenoid, and this is apt to be accompanied by suppuration. In the majority of instances it is necessary to rule out tuberculosis and the neoplasms and this can be done by laryngeal examination, but in many instances laboratory aid must be called in as well. Although gummous new growths are comparatively rare it is certain that in cases of suspected cancer it is necessary to exclude syphilis. The end-results of gummata of the larynx are considerable destruction of tissue and replacement by fibrous tissue, so that much deformity may result if treatment is not begun early. In some cases breathing may be rendered very difficult, and operative interference demanded.

#### SYPHILIS OF THE TRACHEA

It is stated by a number of authors that the secondary eruption of syphilis at times occurs upon the mucosa of the trachea. However, far and away the most important lesion is the diffuse gummous infiltration that leads to stenosis. Gerhardt divides the course of the disease into three stages: that of irritation, that of stenosis, and that of suffocation. The first corresponds to the stage of gummous infiltration, the second to that of organized and permanent contractures, and the final stage to a further narrowing of the lumen. In the first stage the symptoms, in one case I saw with Reede, were a dry and paroxysmal cough of a distinctly brassy





Fig. 44.—A young girl fell from a chair to the floor; within a few weeks a large swelling developed just below the elbow, which was at first thought by the surgeons to be sarcomatous, but the Roentgen rays showed periostitis, which was definitely syphilitic in character.



Fig. 45.—In this advanced Charcot joint, occurring in a tabetic, there were definite syphilitic changes in the periosteum.

character and shortness of breath. The expectoration was scanty and mixed with blood. A well marked inspiratory stridor was present over the sternum. In the second stage the symptoms are dyspnea of an inspiratory type, and inspiratory retraction of the soft tissues near the attachment of the diaphragm and in the region of the clavicle, and an inspiratory stridor which is the most important sign of all. Suffocative attacks are symptoms of the final period. The diagnosis can be made positively and directly by means of the bronchoscope. Differential diagnosis must be made from asthma, tracheal stenosis due to constriction from without, or to cancer. X-ray examination will rule out stenosis from external causes, and also the presence of foreign bodies within the trachea. Laboratory tests positive for syphilis are also of value. The pathologic condition is that of replacement of diffuse gummous infiltration with scar tissue. The prognosis is always serious unless the cases are diagnosed before infiltration is fully established. However, when there are manifestations of the second stage arsphenamine may greatly aid the condition, as in the case that Reede and I saw together. The mortality of the reported cases is over seventy-five per cent. Tracheotomy is not of much value in the treatment because the lesions are usually situated at the bifurcation of the bronchi, and the bronchi themselves are frequently involved.

#### SYPHILIS OF THE LUNGS

Syphilis affections of the lungs still remain a source of much dispute among both clinicians and pathologists; the former consider it fairly common, while the latter consider it very rare.

Pathologically several types may occur. Gummata either single or multiple may occur in the lung, usually in one of the fibrous septa and most often near the hilus of the lung, although occasionally near the pleura. These gummata may be very small or they may be as large as a hen's egg. Their course is that of gummata in general, that is, late caseation, or, even more frequently, fibroid degeneration. A second type is where an interstitial gummous formation occurs, much as in the case of the skin or tongue, and where the miliary gummata are replaced by fibrous tissue, often in thick bands and usually radiating outward from the hilus of the lungs. Lastly there

may be a mixed form, consisting of fibrous tissue formation, gum-mous changes and pneumonic affections, as well as cavity formation and often bronchiectasis.

Clinically there are four types. The latent, the subject of a recent paper by Landis and Lewis, may be commoner than is usually thought. The patients may be well-nourished and show no clinical signs of pulmonary trouble, or they may show indications that are diagnosed as pulmonary tuberculosis in an early form. Usually there is some loss of weight, some cough, with expectoration, and occasionally night sweats and some fever.

A second type of syphilis is where there is a definite local cavity formation, due to the ulceration of a gumma into the bronchi. These cases usually resemble tuberculosis very closely.

The third group consist of the so-called "syphilitic phthisis" cases. In this group there is a progressive fibrocaseous course that cannot clinically be distinguished from tuberculosis.

Still a fourth type is the fibroid one, which is clinically indistinguishable from fibrosis due to any cause.

I am firmly convinced that every case of chronic lung trouble should have a Wassermann performed, and that if it be found positive, or if there be any evidences whatever of lues from either the history or the physical examination, pulmonary syphilis should be ruled out if possible. It is difficult to cure cases of pulmonary tuberculosis but relatively easy to improve instances of pulmonary syphilis. If there be definite evidences of syphilis from either the laboratory or the clinical side and if tubercle bacilli are absent, the patient should receive the benefit of the therapeutic test, namely, arsphenamine. So far in my experience x-ray examination has not proved especially helpful in distinguishing pulmonary tuberculosis from pulmonary syphilis.

#### SYPHILIS OF THE PLEURA

There is considerable discussion as to the occurrence of syphilis of the pleura. It undoubtedly does occur in association with lung syphilis, but as a primary disease it must be extremely rare, although probably not unknown, inasmuch as syphilis affects practically every other organ of the body.

## Section 10

### SYPHILIS OF THE DIGESTIVE TRACT

#### SYPHILIS OF THE SALIVARY GLANDS

Haslund has recently reviewed the literature upon syphilis of the salivary glands in addition to reporting a case of his own. Gerber has written the most complete monograph upon the subject in existence. These two articles give a complete bibliography. It is generally agreed that in the course of acute secondary syphilis the parotid, and more rarely the submaxillary and even the sublingual glands, may swell so as to simulate mumps. The condition, however, is extremely rare. It is due to an acute parotitis, that usually subsides rather promptly upon antisyphilitic treatment. According to Haslund, it is usual for the overlying preauricular lymph gland to be involved as well.

In tertiary syphilis the swelling usually affects one gland only, while in secondary syphilis the affection is almost invariably bilateral, and usually develops slowly and painlessly. As a rule the swelling is adherent to all of the surrounding tissues and hence is usually diagnosed as a malignant tumor. While the parotid is the gland usually affected, any of the other salivary glands may be the site of election. There may or may not be manifest luetic lesions in other organs. Microscopically the lesions are typically gummous.

#### SYPHILIS OF THE ESOPHAGUS

Specific lesions of the esophagus are very rare. Wile says "The pathology of syphilitic esophagitis depends upon the time at which the case may be studied. Secondary superficial erosions and ulcerations, such as occur in the mouth and pharynx are not described in the esophagus. Such cases do not come to autopsy frequently. The not infrequent dysphagia, however, that occurs in secondary syphilis could, I think, well be due to superficial erosive syphilides. The great bulk of our cases, however, are those of tertiary syphilis. Here it would seem that the process is usually a gummatous condition of the submucosa which undergoes one of two changes. It may, under appropriate treatment, or even spontaneously, involute by fatty degeneration. In the event, however, of no treatment, or occasionally, in spite of treatment, such gummatous changes are apt

to undergo early ulceration. If these heal, there results a scar with a marked tendency to contraction and resulting stenosis. Finally there may be, instead of localized scarring and contraction, a diffuse process encircling the entire tube for the greater part of its length and causing almost complete stenosis and impassibility for solid food."

The differential diagnosis may be very difficult, for carcinoma of the esophagus, pressure from mediastinal masses and spastic conditions must be ruled out. In addition it must always be remembered that it is possible that the gummous changes might later become cancerous. Fluoroscopic examination with bismuth in the esophagus is of great value in some instances, and the signs of syphilis in other organs, or the presence of a positive Wassermann would be of considerable value. It is probable that more than one case of syphilis of the esophagus has been deemed cancerous and given up to die, when active measures might have saved a life.

The treatment consists of antisyphilitic remedies and esophageal dilation with suitable bougies.

#### SYPHILIS OF THE STOMACH

Disturbances of the stomach during the early stages of syphilis have not received the attention they merit; the literature on the subject is extremely scanty. However, Neugebauer, with true Teutonic industry, has examined the stomach contents of two hundred syphilitics in the secondary stage and found hypoacidity in 62 per cent, while in 18 there was a marked diminution of free hydrochloric acid. In 17 per cent hyperacidity was discovered. Local treatment of the stomach condition did not improve these findings, but treatment of syphilis was followed by marked benefit. He states that all two hundred patients were healthy before syphilis was acquired.

In twelve years' experience with syphilitic patients I have seen five instances in which intractable vomiting accompanied the secondary lesions, although in no instance did the other symptoms seem to be especially severe. All of the cases cleared up under mercurial injections.

Clinically there are four late types of the disease, first, syphilitic ulcer, second, gummata, giving tumor masses, third, pyloric stenosis and fourth, diffuse infiltration of the wall.

Cases of ulcer have been reported by various observers. Ewald

states that probably 10 per cent of all ulcers are of a syphilitic nature, but Morgan is sure that the figure should be much nearer one per cent. According to Kohn, who has written one of the best articles upon the subject, these ulcers may exist alone, or may be associated with gummata. They may be multiple, although they are usually solitary. The site of predilection is the posterior aspect of the cardia and the pylorus. In shape they may be either round or oval, and in depth they vary from superficial erosions to those causing perforation. "Characteristic for this lesion are thickening of the mucosa and submucosa and nodules of infiltration followed by central necrosis, together with constant finding of endarteritis and endophlebitis." The pathology of the condition is identical with that of tertiary syphilitic lesions in any portion of the body. It is possible that the lesions are not so apt to cause the presence of blood in the stomach contents as are true peptic ulcers.

Tumors have been reported by Kohn, Einhorn, Smithies, Downes and Ewald, and other observers. These growths are usually mistaken for carcinoma, inasmuch as the patients show symptoms that are very characteristic of malignancy. The growths sometimes reach a considerable size before ulceration occurs. The tumors are perhaps most common near the pylorus or upon the posterior surface of the cardia.

Stenosis of the pylorus is, of course, brought about by the contraction of a scar resulting from a gumma, that has either broken down or healed, without ulceration, by fibrosis. Hubbard has recently reported a typical case.

Diffuse sclerosis or cirrhosis is due to a diffuse infiltration of the stomach walls, and may produce varying pictures, the dumb-bell-shaped stomach, a condition similar to sclerosing gastritis, to Brinton's linitis plastica, which in reality may always be syphilitic in nature, to a diffuse carcinomatosis of the stomach wall, to a diffuse hypertrophy of the entire organ on a tuberculous basis, or to a stenosing gastritis. The case reported by Lasfleur still remains classical.

As is to be expected, all cases of syphilis of the stomach show certain things in common, and these have been well worked up by Smithies. The disease is most apt to manifest itself between the ages of thirty and sixty, it is almost as common in women as in men, it is usually a late manifestation, but may appear during the late

secondaries and usually manifests itself rather suddenly without previous digestive disturbances. The laboratory findings generally show some anemia; occult blood in the stool is rare; gastric acidity is usually low.

While time should never be lost in a case of suspected malignancy, still it should always be borne in mind that syphilis of the stomach can give all of the symptoms of cancer, and every patient who is suffering from gastric malignancy should have lues ruled out as a routine procedure.

#### SYPHILIS OF THE INTESTINES

Syphilitic lesions of the intestines are probably more common than those of the stomach, although there is a great paucity of literature on the subject. It is probably commoner in the congenital than in the acquired type of the disease. In a recent article Symmers states: "In six subjects of the Bellevue Hospital series (314) syphilitic lesions of the intestines were present. Ulcerative lesions of the cecum occurred once, and ulcerative and stenotic lesions of the colon five times. In one case the splenic flexure and the descending colon 6 cm. below were ulcerated and stenosed, and in the remaining four cases there were stenotic lesions in the rectum."

#### SYPHILIS OF THE RECTUM

Considering that pederasty is not an unknown practice, chancres of the rectum are extremely rare; very much rarer than chancres of the anus. Lang has examined forty-five men and sixty-five women in the florid stage of syphilis as to the presence of secondary lesions in the rectum and found them in sixteen instances, usually in the form of slight erosions seated upon the posterior wall. In these cases there were few symptoms. There are four types of tertiary lesions: (1) a proliferating proctitis; (2) a diffuse interstitial inflammation known as "anal-rectal syphiloma"; (3) gummous inflammation; (4) diffuse fascial tumor of the pelvis.

The diffuse gummous process usually begins near the anus, and the entire circumference of the bowel is affected. Multiple ulcers may form from the breaking down of several foci. The disease is distinctly more common in women than in men. In the surgical service at Freedmen's Hospital I have seen at least a dozen cases in women and only two in men. The sphincters frequently lose



their tone, and involuntary passage of feces and pus then occurs. The skin outside of the anus usually shows considerable irritation. When this condition heals there is left a ragged condition of the anal folds that has been compared to the wattles of a cock's comb. As healing takes place there is the formation of scar tissue and a stricture gradually forms. The diagnosis can usually be made by rectal examination, the characteristic finding being that the entire wall of the rectum is affected. This finding will usually suffice to rule out cancer. The treatment of these syphilitic lesions, if seen before stricture has taken place, is the general treatment of syphilis, together with local applications for cleansing purposes. Where stricture has occurred the treatment is entirely surgical, either local dilation, or if necessary a colostomy.

#### SYPHILIS OF THE LIVER

The liver is sometimes affected in secondary syphilis, and more commonly in tertiary lues.

*Secondary Syphilis.*—In early syphilis there are two clinical manifestations that must be noted, first, jaundice, and second, acute yellow atrophy.

*Syphilitic Jaundice.*—There are a number of theories as to its cause, first, a syphilitic catarrhal cholangitis; second, due to a condyloma of the bile duct; third, pressure exerted by enlarged lymphatic glands on the portal fissure. Rolleston thinks it probable that it is due to a catarrhal condition of the small intrahepatic bile ducts, and that when the change is excessive it may run on into acute yellow atrophy. It would also seem possible that an autolysis of the liver cells themselves might produce it in some cases at least. There is no proof that jaundice is due to mercury, inasmuch as it is usually cured by the administration of this drug.

Clinically it is about as frequently seen in men as in women, usually comes on suddenly without any special disturbance and coincides with the arrival of the secondary eruption. The jaundice is well marked and tends to become chronic unless there be anti-syphilitic treatment. The liver is usually a trifle enlarged, and the spleen may be palpable, although as will be shown later, this is not especially rare in early syphilis. As a rule the prognosis is good, although in some rare cases acute yellow atrophy may supervene.

*Acute Yellow Atrophy.*—There seem to be no particular features

which distinguish cases occurring in syphilis from those of the ordinary type of acute yellow atrophy. There are two possible causes for this usually, but not invariably, fatal complication. One is direct invasion of the liver by treponemata, or by the action of poisons from extrahepatic organisms, and the other is in the antisyphilitic medication. Acute yellow atrophy is essentially a rapid autolysis of liver substance; it has been demonstrated that both mercury and arsenical preparations can cause autolysis of the liver, so it is possible that in some instances treatment may be the cause, but on the other hand, this complication may supervene in cases that have not been treated, as in one that I saw in Parker's service at the Freedmen's Hospital. Regarding the symptoms Osler states: "The symptoms appear gradually, with loss of strength and appetite and anemia; vomiting and jaundice appear and, later, the cerebral symptoms of delirium, involuntary passage of urine and feces; the urine contains bile, leucin and tyrosin, and seldom more than a week elapses after the appearance of the more serious symptoms before death."

*Tertiary Syphilis of the Liver.*—That syphilis of the liver is by no means infrequent during the late stages of syphilis is evidenced by various autopsy reports. Symmers, who reported 314 autopsies upon syphilitic subjects found syphilis of the liver 105 times.

The following grouping for hepatic syphilis may be used:

1. Where the symptoms suggest portal cirrhosis, or simple chronic peritonitis and perihepatitis.
2. Presenting the features of widespread lardaceous disease.
3. Suggesting tumor of the liver, such as malignant growth, hydatid, or enlarged gall bladder.
4. Imitating suppuration of the liver.
5. Resembling cholelithiasis.
6. Resembling chronic splenic anemia.
7. Where the clinical features resemble hypertrophic biliary cirrhosis.

To these seven groups Osler has added an eighth, where the symptoms are those of leukemia.

Pathologically the following changes may be found in the liver in the course of late syphilis: gummata, cicatrices from gummata, perihepatitis, amyloid change, cirrhosis, thrombosis of the venous system and infarcts. Gummata commence around the blood vessels

just as they do in other organs, and run just the same course, that is, they are later replaced by fibrous tissue, and the extent of this scar tissue depends upon the size and number of the gummata. Cicatrices may produce stenosis of the bile duct, the cystic duct or even the hepatic duct, or the vascular supply may be interfered with so that localized necrosis follows. Perihepatitis may vary between a small localized thickening of the capsule, comparable to a "milk spot" on the pericardium, to a great thickening of the whole capsule, and even cause adherence to the body wall. In amyloid change the liver is enlarged, and resembles the amyloid changes from other causes.

#### SYPHILIS OF THE PANCREAS

Walter-Sallis states that from the standpoint of a pathologic anatomy, there are three forms of this affection: (1) inflammatory, scleroindurative, usually leading to atrophy; (2) gummosis; (3) sclerotic gummosis. As a matter of fact, all of these forms must be simply different degrees of severity of the same gummosis process.

Warthin concludes: "It seems very probable, therefore, that latent syphilis is the chief factor in the production of the form of pancreatitis most frequently associated with diabetes, but that diabetes is not always coincident with severe degrees of this type of pancreatitis."

Rosenbloom has recently reviewed the relationship between diabetes mellitus and clinical syphilis, and after a study of his own cases and of the literature has come to the conclusion that in the vast majority of instances the syphilitic infection is not responsible. Personally, I have found diabetes to be much more common in syphilitic than in the skin cases that come to my office. Unquestionably, diabetes is more common where there is syphilitic disease of the central nervous system than in other types of lues.

# THE DIAGNOSIS AND TREATMENT OF PRIMARY, SECONDARY, LATENT, AND TERTIARY SYPHILIS WITH A CRITICAL REVIEW OF THE LITERATURE\*

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(Received for publication Dec. 7, 1921)

THIS disease was known in the middle ages; it was prevalent in the early colonies; its infectious nature was long known; and yet the actual knowledge of the disease begins with the day when the spirochetes were demonstrated in the chancre and were followed up in the blood and organs of the body by Schaudinn and Höffmann in 1905. Notwithstanding the fact that there are more syphilitics under treatment today than formerly, the disease seems to be on the decline. As I pointed out in a previous article,<sup>1</sup> there is a smaller number of early infections seen in the clinics in recent years and, since that is the only criterion by which we can measure the prevalence of the infection, this conclusion seems reasonable.

The parasite of syphilis is a protozoon of spirillary form and is called *Spirocheta pallida* or *Treponema pallidum*. It is from six to fourteen microns long and 0.3 of a micron wide. Its body is made up of closely set spirals numbering from six to twenty. Under the dark-field microscope it is seen as if rapidly moving across the field, but according to the investigations of Oelze<sup>2</sup> this is due to the moving fluid. The motion of the spirillum is described by him as being a rotary one, but to the eye of the observer it appears as undulating on account of the difference in thickness of the spirals. In the hanging drop, they are seen to make progress with difficulty. The spirochetes are apparently not adapted for motion in fluids, but bore through a more solid medium with ease. That may be the reason they are rarely found in the blood and body fluids, yet the tissues are swarming with them.

The most reliable method of demonstrating the spirochetes is by

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means of the ultramicroscope or dark-field examination. The suspected lesion is gently scraped with a scalpel, but care should be taken not to draw any blood. The little serum that exudes is picked up on a sterile platinum loop and placed on a slide. A small quantity of saline is mixed with it. Under dark-field illumination the organism is seen as a brilliant spiral rapidly moving across the stage on a much darker background. There are several methods employed for the staining of the organisms, but none is as reliable as the dark-field. Oelze,<sup>3</sup> in comparing the various methods, found that with the India-ink method, only  $\frac{1}{12}$  of the number of spirochetes demonstrated by the dark-field could be made visible. With the Giemsa and other stains, only about  $\frac{1}{3}$ . On many occasions, I tried to stain specimens which were swarming with organisms under the dark-field and obtained only doubtful results or none at all.

That spirochetes can live outside of the body for a long time, is demonstrated by the following experimental facts. Lacy and Haythorne<sup>4</sup> were able to successfully inoculate animals with dead autopsy material and serum from chancres twenty-six hours after removal from the body. Spirochetes were found to retain their motility in autopsy material for forty-eight hours and in serum which was obtained from the exudate of a chancre and which was kept in sealed tubes at room temperature, after 121 days. After drying, the results were completely negative. Zinsser and Hopkins<sup>5</sup> showed that spirochetes kept in moisture and exposed to diffuse daylight lived eleven and one-half hours after removal from the human body. Neisser<sup>6</sup> found that syphilitic material loses its power of infection in twenty-four hours if kept at ice box temperature, in three hours at 10° C., and in thirty minutes at 48° C. The same author found that glasses at soda stands used by patients with mucous patches in the mouth retained living spirochetes for thirty minutes after being washed, in the manner prescribed by the board of health. Savnick<sup>7</sup> found spirochetes in the mouth in four out of twenty-five patients with primary lues, in thirty-four out of forty-eight cases of secondary lues, and in five out of thirty-four latent cases.

The spirochetes gain entrance into the body by way of the skin or the mucous membranes, or directly into the blood as is the case in hereditary lues in which instance the germ enters the portal circulation of the fetus directly by way of the umbilical vessels. Occa-

sionally, the point of entrance of the spirochetes cannot be detected. This is the case in the so-called decapitated syphilis in which the primary lesion is absent or in cases where the point of entrance is in the mucous membranes of the body cavities as in the urethra, the vagina, or uterine cervix, and is overlooked. For infection by way of the skin, a solution of continuity is regarded as essential, as for example, ordinary abrasions, itching eruptions causing secondary lesions by scratching, vesicular lesions as herpes, scabies, etc. In the case of mucous membrane infections, a solution of continuity is not regarded as essential. Most syphilitic infections are transmitted by means of sexual contact. A number of cases, however, about one in eight or nine syphilitics, are innocent infections, the chancre appearing on other portions of the body than on the genital tract, notably on the lips, the eyelids, the tongue, the tonsils, and the fingers. Infectious material for the production of the extragenital chancre may be carried by kissing, by the use of infected utensils as drinking cups, also by the use of public toilets, and by the handling of syphilitic patients by physicians and nurses. Cases of infection by chewing gum used by luetics have been reported.

Immediately after infection takes place, the spirochetes begin to multiply and invade the surrounding tissues. They find access to the blood and lymph stream and are widely distributed long before there are any signs of infection. Brown and Pearce<sup>8</sup> found spirochetes in the inguinal glands forty-eight hours after inoculation of the rabbit's testicle with syphilitic material. They demonstrated spirochetes in the blood seven days after inoculation. Reasoner<sup>9</sup> was able to transmit the disease from inoculated to healthy animals seventeen days before the appearance of any signs of infection. He was also able to demonstrate the infectiousness of the blood of an inoculated animal even when the infected testicle was excised long before a primary lesion appeared. Clinically, this early systemic invasion is occasionally evidenced by jaundice and splenic enlargement occurring almost simultaneously with the chancre and disappearing with it during treatment. Five such cases were collected from the literature by Chattelier and Bonnetterre.<sup>10</sup>

If an exposure to syphilitic infection becomes known at the pre-invasive stage,—namely in less than forty-eight hours after exposure, the progress of the disease may be checked by the administration of a full dose of arsphenamine on each of two succeeding days.

After that time, no such thing must be attempted until there is clinical evidence of infection. For one must bear in mind that if infection has taken place there is already a systemic invasion which the latter procedure seeks to prevent. On the other hand an exposure does not always mean an infection. In the army any individual known to have been exposed to infection with syphilis was ordered to vigorously rub in a 30 per cent calomel ointment into the exposed part immediately after the exposure. Guy<sup>11</sup> states that it was effective in every case where this method was used.

After infection takes place, there follows a period during which there are no clinical signs. This is called the first period of incubation. The spirochetes go on multiplying locally at the point of entrance until the first evidence of the disease, the chancre appears. It is needless to waste time by a description of the primary lesion. One point, however, needs elucidation,—namely the appearance of the incipient lesion. This is extremely difficult to see clinically as the patient will not seek advice of the physician for an apparently insignificant and painless sore as the chancre must appear to be during the first few days of its existence. The experimental lesion comes to life either as a minute papule or a little scale appears and when the latter is removed, there is a slight erosion.

With the appearance of the primary lesion, the problem of making a correct diagnosis is of utmost importance. It is needless to state what the failure to diagnose syphilis at this early stage, when the disease is present, means to the patient and to the community. One must not forget, however, that an erroneous diagnosis of syphilis in the absence of the disease means untold suffering to the patient and his family. A diagnosis of a chancre by the clinical appearance of the lesion alone is not deemed safe, even if it is made by the most highly trained specialist. The diagnosis is to be made by the ultramicroscope. In the early lesion, the spirochetes are numerous and their detection is not difficult. Failure to find them on one examination should not be regarded as a negative result, but the examination must be repeated. To facilitate the finding of the organisms no antiseptics should be used, likewise no cauterization, only a wet dressing of a normal salt solution should be applied. In cases where the chancre is inaccessible, or when it is located in the mouth, in which case the finding of the spirochetes is made difficult on account of the numerous nonpathogenic spirillae which are con-

stantly present, also in cases where the germ cannot be obtained from the lesion on account of the application of antiseptics or escharotics, a new method of diagnosis has been recently evolved. Several days after the appearance of the chancre, there is an enlargement of the lymph nodes, first of those that drain the region of the lesion, later the adenopathy becomes general. Freuwald<sup>12</sup> demonstrated spirochetes in the regional lymph nodes in twenty out of twenty-four cases of primary lues and showed that the shorter the time that elapses from the appearance of the chancre the more positive are the findings. Droop,<sup>13</sup> Schultz,<sup>14</sup> and others have utilized the above fact for obtaining spirochetes from the glands for diagnostic purposes by means of gland puncture. The method described by Schultz is as follows: A sterilized 5 c.c. syringe is filled with one-half to one c.c. of sterile normal saline. The gland is firmly held between the first two fingers and the thumb of the left hand. The needle is gently pressed through the skin and then through the capsule of the gland. The point of the needle is rotated so as to break up some of the gland tissue. The saline is injected slowly and the needle is rotated a few more times. The gland is then aspirated and a dark-field examination is made. He claims that he found spirochetes in every case in which this method was used. I have used this method on several occasions with good results. Baelslack and Kean<sup>15</sup> have made a successful attempt to culture spirochetes for diagnostic purposes. A piece of tissue is excised from a chancre to which antiseptics or escharotics have been applied and which was made useless for diagnosis by ordinary means. The piece of tissue is incubated in a special culture medium at 37° C. from three to five days and the medium adjoining the tissue is used for a dark-field examination. They report many positive cases.

During the process of growth of the organisms in the initial lesion, their invasion of the blood, and their localization in the organs of the body, especially in the skin, a biochemical reaction takes place which has a lethal or repressant effect on most of the organisms at the point of localization. Probably antibodies are produced in the lesion by a reaction set up against the germ colonies which may have been carried there by the lymph or the blood stream. For that reason, the tendency is for the spirochetes to disappear from the lesions and for healing of the lesions spontaneously without treat-



ment. Accordingly, in the third week of the chancre, spirochetes are rarely found. At the same time, we are deprived of the diagnostic value of the Wassermann test, for the latter remains negative in a majority of the cases up to the fourth week. Lloyd<sup>16</sup> found the Wassermann reaction positive in 30 per cent of the cases ten days after the appearance of the chancre. This proportion increases gradually until the fifth week, when the percentage of positive reactions is 100. Klauder and Kolmer<sup>17</sup> found uniformly positive Wassermann reactions in fluids collected from chancres. This may be used for diagnosis before the blood reaction becomes positive. Disregarding all advantages to the patient from early treatment, the physician must be warned against commencing the same before an absolutely positive diagnosis is made. A negative Wassermann reaction in a patient with a suspicious lesion older than two weeks calls for another, and a third test, until a positive reaction is obtained or till such time when a negative reaction has its diagnostic significance.

As soon as the diagnosis is established, treatment must be started immediately. The drugs used are arsphenamine and mercury. Preparatory to the administration of arsphenamine, the patient is ordered to take a saline purgative the night before. If the treatment is to be given in the afternoon, a light breakfast is allowed and only a cup of tea or coffee for lunch. The method of choice is the double tube gravity apparatus. The advantage of this method is that one of the glass tubes is filled with water and, after the insertion of the needle, the water is first allowed to flow into the vein and only after the operator is certain of a free flow, the latter is shut off and the arsphenamine solution is permitted to flow. In this manner, any possible chance of infiltration of the subcutaneous tissues with arsphenamine is prevented. The contents of an ampule of arsphenamine is put into a dry sterile flask, is shaken for a few minutes to break up the lumps into a fine powder, then warm water is poured over it, and the solution is completed by gently agitating the mixture. The solution is strongly acid in reaction and it must be neutralized with a 15 per cent solution of sodium hydroxid. At first, about ten drops are added at once, then drop by drop until the milky liquid becomes perfectly clear again. Slight overalkalinization is said to make the solution less toxic. It is important to avoid unnecessary shaking of the neutralized solution as the latter pro-

cedure tends to increase its toxicity. The needle should not be larger than 20 gauge and the flow not faster than 0.1 gm. per minute or not less than five minutes for the full dose. Roth<sup>18</sup> tested the toxicity of arsphenamine experimentally on animals and found that it is more toxic under the following conditions: (1) insufficient neutralization; (2) concentrated solutions and, if the latter is also acid in reaction, it is very toxic; (3) when a solution is rapidly injected its toxicity is markedly increased; (4) samples that do not dissolve readily or completely; even though the undissolved part is filtered out; (5) vigorous shaking of a solution of arsphenamine after it has been neutralized or a solution of neoarsphenamine in the presence of air, changes its color to a darker shade on account of the formation of an arsenoxid which increases its toxicity many fold; (6) strong garlicky odors and changes in color indicate a high toxicity. From personal observation, I can add that inability to completely clear a solution after neutralization makes the preparation completely useless on account of its high toxicity.

Kolmer<sup>19</sup> tested the hemolytic activity of arsphenamine and neoarsphenamine and found that all solutions of arsphenamine are hemolytic, but if the drug is dissolved in an isotonic salt solution it is three to ten times less hemolytic and that practically the same conditions described above as increasing the toxicity also increase the hemolytic activity of the drug. In spite of the above facts, plain sterile distilled water is generally used today for making arsphenamine solutions. Neoarsphenamine is not hemolytic in concentrated solutions, but is hemolytic in dilute solutions of 0.1 gm. to 10 c.c. of water. This is due to the hypotonicity of the solution. It may be completely avoided by using a normal saline instead of water. The cause of the toxicity of arsphenamine is still a disputed question. While many writers hold that it is due to arsenoxid, a product liberated by the splitting of the arsphenamine molecule, Reid Hunt<sup>20</sup> points out that arsenoxid can be completely neutralized by sodium hydrosulphite without, in the least, diminishing the toxicity of the product. Schamberg<sup>21</sup> calls this toxic substance the toxic principle X. He found that it is only capable of producing severe nitritoid reaction in men, but not in rats.

Neoarsphenamine can be used in concentrated solutions, a full dose in ten to twenty c.c. of water. In fact, as pointed out above, if water is used as a solvent, it is less hemolytic in a concentrated than

in a dilute solution. For its administration, a syringe may be employed, although that method has its disadvantages. It happens not infrequently that the piston gets stuck and does not move freely. This makes it necessary to force the piston into the barrel of the syringe and if the vein is small or concealed, the needle may be pushed through it causing infiltration. The aspiration of blood into the syringe is not an absolute means of ascertaining that the vein has been properly entered, for blood may be aspirated from a perivenous effusion caused by injury to the vein. If blood has been aspirated into the syringe and for some reason or other the vein has to be abandoned and the injection is to be made into another vein, the solution is already sufficiently dark from admixture of blood to make a second aspiration almost useless.

The vein to be selected is either the median cephalic or the median basilic, but any vein in the forearm may be chosen. At times, one may be forced to pick a vein in the arm or on the back of the hand if it happens to be sufficiently large. I rarely found one in the foot large enough for the purpose, except varicose veins which, in my estimation, should never be tampered with. I was, however, quite successful in giving intravenous injections into the external jugular. The method employed is as follows: The patient is placed on his back with his face turned as far as possible to the side opposite the vein selected. He is ordered to exhale forcibly with his mouth tightly closed. This brings the vein into prominence. With the intelligent cooperation of the patient, this method is not any more difficult than the ordinary intravenous. There are times, however, when the intravenous route must be abandoned on account of the lack of suitable veins. In these cases, rectal injections may be resorted to. I had excellent results in a number of cases of florid syphilis and encouraging results are reported from many sources. Grajefsky<sup>22</sup> says that the results from treatment with this method are as good as with any other method and that he never saw a reaction after its use. Mehrtens<sup>23</sup> finds that the old arsphenamine is too irritating and he uses massive doses of neoarsphenamine, 4.0 gm. per dose. He treated 125 patients by this method and came to the conclusion that the results are fully as good as from the intravenous treatment. Arsenic persisted longer in the blood and there was three times as much arsenic excreted in the urine after rectal than after intravenous injections.

The value of nearsphenamine as compared with the older product has been satisfactorily demonstrated by Schamberg and his staff of assistants<sup>24</sup> by animal experimentation. They have shown that the older product is 1.74 times more trepanocidal than nearsphenamine, while the maximum dose of the latter has, by 50 per cent a greater margin of safety in rats than arsphenamine. One point must be made clear, namely, that the therapeutic value of the arsphenamine preparations is dependent upon those particular chemical combinations and not simply upon their arsenic content. There are other drugs rich in arsenic as, for example, cacodylate of soda, which have been proved to possess absolutely no value as therapeutic agents in syphilis. On the other hand the arsphenamines have been tried in psoriasis and, according to the reports in the literature, without any success, although arsenic in the form of the trioxid is of recognized merit in that disease. The chemical action of the arsphenamines is said to be as follows: the arsenic becomes attached to the spirochetes by means of the benzene group and causes their destruction.

From recent experimental studies with salvarsan and mercury, Wassermann<sup>25</sup> came to the conclusion that salvarsan is purely spirocheticidal and that mercury acts on the cells which have been changed by the poison of the disease and also on the inversion of the lipid metabolism. Stokes<sup>26</sup> says that mercury is not spirocheticidal, but as a stimulant of immunity it is superb. The quantity of mercury that can be introduced into the blood with safety is not large enough to have any spirocheticidal action when it becomes mixed with and diluted by the body fluids. Schamberg<sup>27</sup> states that the therapeutic dose of arsphenamine is infinitely more destructive to spirochetes than the therapeutic dose of mercury. This is substantiated by facts on experimental animals. Kolmer<sup>28</sup> found that arsphenamine will kill treponema in a dilution of one in 40,000. Guy<sup>29</sup> found spirochetes in a chancre twenty-two hours after mercury injections, while no organisms were found one and one-half hours after a full dose of arsphenamine.

There are several methods in vogue for the treatment of syphilis. They range from the intensive or so-called abortive method to the medium dosage administered at long intervals. In choosing the mode of procedure, one must take into consideration the effect desired. For a powerful action on the spirochetes, which is important

in early lues, the former method is the one to be chosen. In late syphilis, where the spirochetes are lodged in fibrosed areas and are not accessible to drugs either in the blood or in the tissues, the immunizing action is the one most desired and the latter procedure is the one to be preferred. The various methods are as follows. (1) Abortive or intensive treatment advocated by Pollitzer.<sup>30</sup> One full dose of arsphenamine is given on each of three successive days and is followed up by a course of mercury of ten weekly injections. After a period of rest, the course is repeated. About three such courses are given in primary lues and four or more in the secondary stage of the disease. One advantage claimed for this method is that it shortens the period of infectiousness. (2) Rieger and Solomon<sup>31</sup> have gone even further in this direction. They give 0.9 gm. neoarsphenamine as a first dose, a second dose of 0.6 gm. is given one hour later, and a third dose of 0.3 gm. is given at the end of the third hour. They assert that they have never seen any ill effects from it. (3) Schamberg<sup>27</sup> gives 0.4 gm. arsphenamine twice a week and as many as fifteen doses. (4) Stokes<sup>26</sup> gives three full doses during the first nine days, followed by weekly injections of milder doses until six to eight doses are given. (5) The method employed by most of the workers in syphilis and in old luetics by all syphilologists is the moderate weekly dose according to the tolerance of the patient. None of the above described courses can be accepted as standard for all cases of syphilis, for here as well as elsewhere in medicine, it is the patient that should be treated and not the disease. In determining how intensive a treatment a syphilitic should receive, one must estimate the general condition of the patient, the absence of cardiovascular disease, the state of the liver, of the kidney, and the susceptibility of the patient to arsenic. One can take greater chances with the patient in the hospital than at home and greater chances with a patient who stays at home during the beginning of the treatment than with one who comes to the office and walks the streets afterwards. In general, it may be said that the intensive treatment is of value in very early cases, when the spirochetes are still accessible in the blood and tissues. Here the daily doses are important as the arsenic rapidly disappears from the blood after the injection. As has been shown by Swift and Ellis,<sup>32</sup> blood drawn one hour after the injection of a full dose of arsphenamine contains only 0.016 mg. of arsphenamine per c.c. of blood, and six hours

after the injection they found no spirocheticidal action in the blood serum at all. In old cases, we cannot expect to kill off all or most of the germs with the massive doses and therefore the slow method is chosen, for its immunizing effect. Even here the spirocheticidal action of the arsphenamine is not entirely sacrificed.

The dose likewise cannot be standardized, because, outside of the action of the drug, there are other factors entering into the question of the treatment of syphilis, namely, spirochetal individuality and the personal factor of the host. In general, it may be said that 0.1 gm. for every twenty-five pounds of body weight for men and 0.1 gm. for every thirty pounds for women and children constitutes a therapeutic dose. It has been pointed out by many observers that there is danger of starting the treatment with small doses of arsphenamine for fear of developing a strain of spirochetes immune to the drug. While Katz<sup>33</sup> states that half the maximum dose of arsphenamine kills surface spirochetes as efficiently as the full dose, Shaffer<sup>34</sup> found clinically that daily injections of 0.1 gm. of arsphenamine for a long period had no effect on clearing up secondary lesions. Okatsu, Seinaï, and Noguchi<sup>35</sup> were able to decrease the tolerance of spirochetes for arsphenamine five to six fold by gradually increasing the amount of the drug in the culture medium. With this experiment, Noguchi placed Fournier's clinical observation, namely, the necessity of intermittent treatment and of giving the patient a period of rest between the treatments, on a scientific basis. On the other hand, when massive doses are used alone, the spirocheticidal action is powerful, but there is no process of immunization going on in the system and there is danger of neuro-recurrences. The spirochetes remaining after the onslaught of the massive doses of arsphenamine, in the absence of a resisting mechanism in the system, rapidly recuperate and cause further invasion. Ehrlich advocated more salvarsan for that danger, not for its spirocheticidal effect as much as for its power of stimulation of immunity by smaller doses at longer intervals. As has been seen, arsphenamine cannot be used for a long period at a time for two reasons; its immunizing effect on the spirochetes against the drug itself, and also on account of the toxic action on the body if its use is unduly prolonged. For that reason we must have recourse to another drug to fill the gap between courses of arsphenamine treatment, and that drug is mercury. Saboured<sup>36</sup> found that patients who had a long

course of mercury did not have a recurrence of the positive Wassermann reaction, while those treated with short courses of arsphenamine alone had recurrence. One may ask why should mercury not be relied upon entirely? It is because its action is slow where speed is urgently needed and its toxicity is great especially in prolonged administration. Stokes<sup>26</sup> says that one wonders whether massive mercurialization does not wreck the system as it "cures" the disease, whereas, arsphenamine, discriminately used, has a tonic action, giving inexpressible relief from the depression of mercury treatment. Schamberg<sup>27</sup> states that the therapeutic dose of arsphenamine is infinitely more destructive to spirochetes than a therapeutic dose of mercury, that fatal cases have occurred from the use of both drugs, only in the case of mercury the process is slower and therefore less incriminating.

A chemical compound, in order to be of practical value in the treatment of an infectious disease, must have a greater affinity for the parasite than for the body cell and the greater the difference in this affinity the greater is the value of the drug. Powerful drugs bring about some changes in the cells of certain organs. When they are mild no material interference with the function of the organ takes place. When there is serious damage, organic insufficiency and even death may be the outcome. In treating a chronic disease like syphilis, drug administration is necessarily prolonged and repeated damage to the organs, unless carefully watched, may lead to unfortunate results. According to Kolmer and Luke<sup>37</sup> hydrogen-ion in acid arsphenamine and hydroxyl-ion in alkaline arsphenamine cause the severe changes in the tissues. Neoarsphenamine has one of its amino groups closed and is neutral in reaction, therefore it is half as toxic as arsphenamine. After exhaustive studies on experimental animals, they came to the conclusion that the arsphenamines have a special affinity for the liver, the adrenals, and the blood vessels. Mercury has a special affinity for the kidney and the brain. The last is an entirely new observation by the above authors. Intolerance of the system to the drug is manifested in the form of more or less severe acute reactions or signs of chronic poisoning.

Of the acute reactions to arsphenamine, the nitritoid crisis which was designated by Milian, also called table reaction or immediate reaction, occurs during the administration of the drug or immediately after. It is characterized by redness of the face, dyspnea, a

feeling of anguish and distress, cough, and precordial pain. This is accompanied by a marked lowering of the blood pressure. The early reaction which was designated by Schamberg and Raiziss may occur one or two hours after the administration of the drug or at any time within the first twenty-four hours. Its characteristic signs are chills or chilliness, headache, nausea, vomiting, diarrhea, and a rise in temperature. Kolmer and Luke<sup>37</sup> point out that the nitritoid reaction with its fall in blood pressure and the vasoparalysis may be due to the action of arsphenamine on the cells of the suprarenals, by causing a diminution of the adrenal secretions. Norimasa Hirano<sup>38</sup> studied this anaphylactoid reaction in rabbits. He extirpated the suprarenals after administering a mild dose of arsphenamine and found them nearly normal, but after a large dose he found only a weak chromatin content. The bilateral epinephrin content in normal rabbits is 0.2 gm., after large doses consisting of six or seven milligrams per kilo of body weight, it was only 0.116 mg., and after mild doses of two or three milligrams per kilo there was only a slight decrease. After neoarsphenamine the decrease in chromatin was much smaller. This lowering of the chromatin content gradually diminished and the quantity was again normal within twenty-four hours after arsphenamine and within two hours after neoarsphenamine. He explains the reaction in the following manner. Some of the arsphenamine combines with the epinephrin in the circulation and causes an immediate reaction, while the balance finds its way to the adrenals, combines with the epinephrin in that location, and in that manner perpetuates the condition. The reaction may be checked with comparative ease by the administration of ten c.c. of adrenalin hypodermatically as soon as signs of it appear and it can be prevented in susceptible patients by giving the adrenalin just before the intravenous injection of arsphenamine. Busman<sup>39</sup> employs the following method for the prevention of the anaphylactoid reaction: (1)  $\frac{1}{50}$  gr. atropin is injected hypodermatically twenty minutes before the dose of arsphenamine, (2) he induces antianaphylaxis by injecting  $\frac{1}{10}$  of the dose of arsphenamine twenty minutes before the balance of the full dose is given, (3) he combines both methods in very sensitive patients. At twenty minute intervals, first the fractional dose of arsphenamine, then the atropin, and last of all the full dose of the drug is given.

Precipitation is considered by some a cause of reaction after ars-



phenamine medication. In 1910, Michaeli<sup>40</sup> suggested that a precipitate which forms in the serum after arsphenamine injections may be responsible for reactions and fatalities. Bermann<sup>41</sup> thought that the precipitate is a protein substance and suggests that the increased protein content in the blood in some syphilitics may favor precipitation *in vivo*. He tested the serum of eleven syphilitics who had nitritoid reactions after the drug and found that their blood formed precipitates with arsphenamine in the test tube. Neisser, Schottmuller, and Joseph<sup>42</sup> found precipitation with acid arsphenamine only. Schamberg<sup>43</sup> and his associates corroborate the findings of the last mentioned authors and state that the precipitate is not a protein, but the drug itself. The latter is proved by the fact that it dissolves readily when a drop of alkali is added to it, which is impossible in the case of a protein. They showed that precipitation cannot be a cause of reaction, because neoarsphenamine never forms a precipitate with serum, yet it is quite capable of causing nitritoid reaction. Neisser<sup>44</sup> thinks that the reaction is due to a splitting up of the spirochetes with the liberation of endotoxins. The same thought is expressed by Martin.<sup>45</sup> Stricker and Munson<sup>46</sup> were able to contradict the above assumption by administering the same dose of arsphenamine under the same conditions to two groups of one hundred each of syphilitic and nonsyphilitic individuals and by finding the same percentage and the same kind of reactions in each group. They believe that chemical impurities, as small amounts of sulphur constantly present in the preparation and also the reaction between the drug and the chemical constituents of the blood, may be responsible for the reaction. Rieger<sup>47</sup> states that arsphenamine may decompose in the solution or in the ampule with the liberation of arsenous acid or a cacodyl-like body. It is a fact that preparations that have passed the government laboratory tests for toxicity as being safe may become toxic in the ampule.

Three factors enter into the causation of a reaction: the chemical compound, the patient, and the technic. The first has been fully discussed. The latter two remain to be taken into consideration. That the mental state of the patient is a factor in causing reaction is evidenced by the fact that they often get reactions when other drugs which are usually harmless are used intravenously. It cannot be estimated how much a faulty technic contributes to the cause of the reaction. The fact that fatalities are rarer now than

formerly and that the reactions reported are fewer in number and milder in character, may be due to a more perfected chemical product or to a better technic. Gennerich<sup>48</sup> believed the reaction to be due to the saprophytes in the water; Wechsellmann,<sup>49</sup> to bacterial proteins in the water. Golay<sup>50</sup> points out that small particles of arsphenamine may be left sticking to the glass even after repeated washings. The arsphenamine becomes decomposed and is reinjected with the next treatment. I find this to be especially true when the syringe is used. Stokes and Busman<sup>51</sup> blame new rubber tubing for the reaction.

Among the other reactions to arsphenamine, are the arsenic eruptions. During the course of treatment of a syphilitic, eruptions may occur, but not all of them are due to arsphenamine. A recurrent secondary eruption may appear, although not very frequently. I only saw one case among several thousand patients. There may be intercurrent eruptions due to other causes than syphilis. Milian<sup>52</sup> describes an eruption which occurs on about the ninth day of a course of treatment. It is an infectious erythema which may be either scarlatiniform, morbilliform, or polymorphous. He thinks that it has nothing to do with arsenic intoxication, but it is due to a lighting up of a latent infection. The real toxic erythema is rare and is associated with vasodilatation bordering on purpura. Neisser<sup>53</sup> describes two types of eruption: an exanthem which occurs after the last treatment of a course, is macular, is accompanied by itching, and ends in a week or two by desquamation; a papulourticarial or an erythematourticarial rash which appears almost after every injection and ends without desquamation is allied to the immediate reaction and may lead to exfoliative erythroderma. Nicolas and Massia<sup>54</sup> describe a rare eruption starting with an erythema, soon becoming papular, then vesicular and bullous, and finally presenting a picture of pemphigus foliaceus. Recovery takes place within two months. Moore and Keidel,<sup>55</sup> Labbe and Langlois,<sup>56</sup> Esbach,<sup>57</sup> and Gorke<sup>58</sup> describe an aplastic anemia as a rare complication of arsphenamine treatment. There is an anemia with leukopenia, a diminution of the proportion of polynuclear leucocytes, a diminution of the platelets, delayed coagulability of the blood, and almost a complete absence of leukoplastic bone marrow cells. The blood picture of exfoliative dermatitis is identical with it.

Jaundice, during the course of syphilis, may be due to the disease,

it may be coincidental, or it may be due to the arsenic. True syphilitic jaundice occurs before treatment is started and is due to a parenchymatous degeneration of the liver caused by the spirochetes. It may be due to a combined action of the spirochetes and the arsenic treatment as a sort of Herxheimer reaction which phenomenon will be explained later. A catarrhal toxi-infectious jaundice has been described as a rare occurrence. It is secondary to arsenical gastroenteritis. Real toxic jaundice is due to structural changes in the liver, induced by the arsenicals, and has a tendency, in some cases, to go on to the development of acute yellow atrophy. Kolmer and Luke,<sup>37</sup> also Warthin<sup>59</sup> found in cases of arsenic poisoning areas of focal necrosis in the liver, which were filled with spirochetes, a Herxheimer reaction. It cannot be denied that jaundice during the course of syphilis, as well as acute yellow atrophy is more common since the introduction of arsphenamine. The reason for this is that a large amount of the drug passes directly through the liver and causes damage to the cells. This is made possible by the special affinity of arsenic for the liver cells. Spirochetes may lodge in the weakened areas and cause further damage.

The danger signals that may appear during the treatment of a patient with arsphenamine are (1) itching, appearing shortly after the injection and lasting twelve to twenty-four hours, (2) substernal pain, dull and persistent, is an indication of arsenic intolerance or oncoming dermatitis exfoliativa, (3) an exanthem. Treatment should be discontinued for six months if any one of these appears. One must always bear in mind that in fighting the spirochetes there is the possibility of injuring the patient. Bailey and MacKay<sup>60</sup> found hypercholesterinemia as a constant early sign of toxic jaundice. I had only two cases of jaundice developing during the course of treatment with arsphenamine and mercury among a large number of syphilitics. Unfortunately, both were lost sight of before any definite conclusions as to the outcome could be drawn. In examining the literature on the subject, we find that some workers report much higher percentages of toxic jaundice as a complication of the arsphenamine treatment than others. Schamberg<sup>27</sup> believes that the bad results are due to the combined treatment of arsphenamine and mercury and that with arsphenamine alone the results are not so bad. He quotes Wechselmann<sup>61</sup> who had 59 cases of toxic jaundice after intensive combined treatment and he found kidney complica-

tions in every one of them. On account of the kidney injury by mercury, the elimination of arsenic is interfered with. The liver being the chief reservoir for arsenic, is the first injured during faulty elimination. Too long a residence in the liver causes arsphenamine to be broken up with liberation of the arsenic radical or its oxidation into an arsenoxid. Schamberg urges that the two drugs should not be used together, but courses of one should alternate with courses of the other and if used together the doses of each should be in inverse ratio. The same view is expressed by Almkvist<sup>62</sup> and by Bailey and MacKay,<sup>60</sup> the latter authors also urge a lowered protein diet and a diminution of all exercises during the combined treatment. Broque,<sup>63</sup> recommends in especially susceptible individuals intramuscular injections of arsphenamine as the arsenic in this case does not enter the liver as directly as by the intravenous route. An intelligent estimation of the cause of the jaundice is important in every case. When it is produced by the spirochetes, treatment with arsphenamine is indicated. Even in cases where the jaundice is ascribed to a Herxheimer reaction or a flaring up of visceral syphilis from arsphenamine treatment, the latter is not necessarily discontinued, but it must be used very cautiously and when the occasion demands, it should be temporarily discontinued.

The daily amount of mercury sufficient for absorption and elimination is from six to ten milligrams. This can be obtained from inunctions or from injections of either soluble or insoluble mercury preparations. Recently a strong opposition grew up against the use of the insoluble mercury preparation especially if used in conjunction with arsphenamine. Stokes<sup>26</sup> opposes the use of insoluble mercury during combined treatment, because it may be cumulative and may cause kidney injury. The same thoughts are expressed by Schamberg<sup>27</sup> and by Lomhold.<sup>64</sup> Cole, Littman, and Sollmann<sup>65</sup> injected various mercury preparations intramuscularly and then x-rayed the patients and found that the absorption of gray oil is not constant and hence dangerous, that calomel is not as reliable as mercury salicylate, and that absorption is not equal in all patients, and therefore patients who are treated with insoluble mercury preparations must be carefully watched. While practically all observers agree on the necessity of abandoning gray oil as a therapeutic agent in syphilis, they differ in their opinion as to whether

the salicylate or calomel is the more reliable drug. Lomhold<sup>64</sup> and Schamberg<sup>27</sup> prefer calomel, while Cole<sup>65</sup> and his collaborators point to the salicylate as the more reliable preparation. For the suspension of insoluble mercury preparations, olive oil is preferable to liquid vaseline as the latter is not absorbed readily.

The elimination of the soluble mercurials, as has been demonstrated by Duret,<sup>66</sup> begins within twenty-four hours for the benzoate, and after thirty-six hours for the bichlorid. After calomel, mercury begins to appear in the urine not sooner than three days after the injection.

The comparative value of arsphenamine and mercury has already been fully discussed. It remains to be seen here what is the modern opinion on the curative value of the latter drug in syphilis. Nelson and Anderson<sup>67</sup> treated a series of fifty cases with mercury only. Each patient had a weekly injection of  $1\frac{1}{2}$  gr. of the salicylate. The course lasted from twelve to twenty weeks. Only two patients had a reversal of their reaction from positive to negative, the latter remaining so from two to three months. Twenty-five syphilitics were treated by Haller<sup>68</sup> with mercury only, long enough for all to give a negative Wassermann reaction. All of them became positive again in from nine days to four months. Goodman<sup>69</sup> treated fifty-seven patients who had a plus-four reaction, with mercury only. They each had six to eight weekly injections of one grain of mercury salicylate. In only 9 per cent of the cases the blood became negative. Four per cent of those that were negative after the course, were again positive after the rest period. Better results were reported by Simmons and Johns<sup>70</sup> who obtained a negative reaction in 30 per cent of their cases after treatment for  $2\frac{1}{2}$  months with the oxycyanid. The average amount received by each patient was 14 c.c. of a one per cent solution. The statistics on the subject of treating patients with mercury alone are, of necessity, very limited, as of late years it is hardly done, except in cases where there is a special reason or for experimental purposes. Comparing the above figures with the results obtained from the combined treatment, the marked difference becomes evident. In a previous paper I have shown the results of treating patients with combined courses of five arsphenamine injections of only 0.2 gm. each and ten weekly doses of one grain each of mercury salicylate. The percentage of negatives obtained was sixteen after the first course and thirty-one

after the second course. When larger doses, ranging from four to six decigrams were used, the results were 22.5 per cent after the first course, 44 per cent after the second, and 52 per cent after the third course. The two series included a large number of syphilitics up to thirty years from the date of infection.

In giving mercury injections the following precautions must be taken. The patient must avoid excess of tobacco and must use the tooth brush frequently. The patient's mouth must be examined before every injection on account of the danger of stomatitis and the urine must be tested frequently. Kolmer and Luke<sup>71</sup> found in the experimental animal who received six weekly injections of small doses of mercury, granular and hyaline casts in the collecting tubules, vacuolated cells and shrinkage in the convoluted tubules, and a mild connective tissue proliferation. They found a distinct perivascular infiltration in the brain and milder changes in the spleen, liver, and heart. The changes were proportional to the amount of mercury and not to the route of administration or to the preparation used. Mercurial stomatitis is another very troublesome and often serious complication. I saw a case of mercurial stomatitis with ankylosis of the jaw after five injections of one grain each of mercury salicylate. Gerard<sup>72</sup> points out that in the severe and fatal cases of mercurial stomatitis, the infection of Vincent plays a prominent part. In a protracted case of mercurial stomatitis under my care, a positive diagnosis of Vincent's angina was made. The case started with a mild gingivitis, but after several weeks, developed typical ulcerations of Vincent's angina with positive bacteriologic findings. In the ulcerations of mercurial stomatitis and colitis, there are numerous bacteria which Almkvist<sup>73</sup> found not to be specific, but albumen decomposers. They produce in the erosions hydrogen sulphide, which combines with the mercury, producing a mercury sulphide. The latter is deposited in the cell, causing a drying of the fluid and coagulation necrosis. Thus a fertile field is produced in which bacteria multiply, become more virulent, and soon attach healthy tissues. Gaucher's<sup>74</sup> theory of the causation of mercurial stomatitis is that a chlor-albuminate-peroxide of sodium and mercury is formed. That substance does not circulate freely and is an irritant, causing inflammation. He recommends drinking of sulphurous water to convert the compound into a soluble mercury sulphate which is readily eliminated. Irving<sup>75</sup> used a teaspoonful of sublimed sul-

phur at night in cases of mercurial stomatitis with excellent results.

Eruptions after mercury, have been reported by Fisher,<sup>76</sup> Wechselmann,<sup>77</sup> and Neisser.<sup>78</sup> The rash is described as resembling measles. It is brick-red in color, soon becomes violaceous, then changes to a vesicular eruption which sometimes resembles zoster. Occasionally, the rash is scarlatiniform. All writers agree that it is impossible to differentiate between a mercury and an arsenic eruption and warn against designating every rash occurring during the course of combined treatment as due to arsenic.

The concentration of mercury in the tissues is too small to be directly spirocheticidal. The only action that can be ascribed to it is the stimulation of the bactericidal forces of the host by the formation of antibodies. Noguchi<sup>79</sup> found agglutinins and complement-fixing bodies for culture spirochetes in the serum of immunized rabbits. Kolmer,<sup>80</sup> Nakano,<sup>81</sup> and Kissmeyer<sup>82</sup> found agglutinins for rabbits in culture spirochetes and also agglutinins in 50 per cent of syphilitic sera examined. Eberson<sup>83</sup> found spirocheticidal properties in the serum of patients whose blood gave a negative Wassermann reaction after treatment. His experiments were conducted as follows: He incubated a mixture of virulent and culture spirochetes with serum taken from syphilitics in various stages of the disease and inoculated healthy rabbits with it, and found spirocheticidal properties in the last-mentioned class and also in untreated cases of latent lues whose infection dated back three to twenty-five years, in patients whose Wassermann reaction was so weak that it was only positive with a cholesterin antigen, and in such infants of whom their mother's serum was found to possess spirocheticidal properties. Eberson concludes that protective substances are developed when the infection has attained a period of latency. At a recent meeting of one of the dermatological societies of this city, Pollitzer made a very interesting statement in connection with the subject of immunity in syphilis. He said that of the patients treated by the intramuscular method in the early salvarsan days, those that developed a local abscess as a reaction had a reversal of their Wassermann reaction to the negative after a single injection, and that they remained negative both clinically and serologically for an indefinite period. Possibly, antibodies were formed which were quite capable of coping with the situation.

It is a well-known fact that there is a tendency for the syphilitic

to resist reinfection with the same disease. That resistance begins several days after the appearance of the chancre and becomes fully developed after all symptoms have disappeared, during the period of latency. Why it should be possible for the disease to spread from within, but impossible for infection to be brought from without is not known. This resistance to reinfection becomes weaker during the late tertiary period. It is known that patients with hereditary lues may subsequently acquire a second infection with syphilis. The general opinion is that reinfection can only occur in any instance after the disease has been eradicated either by treatment or by a lapse of time. The same resistance to reinfection has been demonstrated in all other diseases caused by spirochetes. Relapsing fever can be mentioned as a typical example. The difference between this immunity and the one following other bacterial diseases is that the protective mechanism is fully developed while the germ resides in the body and wears off with the expulsion of the latter. This phenomenon is analogous to that found in other infections that tend to assume a carrier stage. Latency is common in typhoid, diphtheria, malaria, and tuberculosis.

There is no positive proof for the generally accepted belief that reinfection is evidence that the patient has been cured of his previous infection. On the contrary, recent experiments by Brown and Pearce<sup>84</sup> seem to disprove it. They inoculated a number of animals with syphilis. Eighteen days later, one-half of the total number of animals infected were treated with 6 mg. arsphenamine or 9 mg. neoarsphenamine. This dose is subcurative in animals. Five days after the treatment, all animals were reinoculated with syphilitic virus. All treated animals, and none of the untreated ones, developed a chancre at the site of the second inoculation, proving that, in animals, reinfection is possible even though the treatment is subcurative and spirochetes are present in the system.

As has been pointed out before, the chancre will disappear even without treatment within a few weeks. With treatment, however, it tends to disappear very rapidly, sometimes after a single dose of arsphenamine. If the patient remains untreated, there follows a latent period lasting from six to ten weeks. During this period, the invasion of the tissues of the body by the spirochetes progresses steadily, and the microorganisms tend to localize in the viscera and, especially in the skin giving rise to the secondary eruption. In



these areas of localization, numerous antibodies, which are inimical to the growth and especially to the further invasion by the spirochetes, are probably formed. This tends to arrest the further progress of the disease. The spirochetes disappear from the lesions, except from those in certain organs, as the lymph nodes for which the germs have a special affinity. The lesions disappear without leaving any evidence of their former existence. From that time on the patient may go on for many years without presenting any clinical evidence of the disease, yet the patient harbors spirochetes and is capable of infecting others. This is called the latent stage. When treatment is started early in the primary stage, the secondary syphilitic eruption is eliminated, and it appears reasonable to suppose that true latency never takes place and if treatment is not vigorous enough or continued long enough to kill off all or most of the spirochetes, late complications are the result, because there is no immunity developed in the system against the spirochetes. Engmann and Eberson<sup>55</sup> cite a case of a physician who was accidentally inoculated. He received two courses of arsphenamine and mercury and his Wassermann reaction became negative. There were no secondaries, as the treatment was started before the latter appeared. He discontinued treatment and, after a lapse of one year, returned with a macular eruption. I saw a similar case at Cornell. What probably had happened, in these cases, is that the treatment aborted the systemic invasion, but did not cure the disease and a new body invasion, which was delayed for a time, took place. A series of experiments on animals by Brown and Pearce<sup>56</sup> bear out the contention that suppression of the primary lesion without curing the disease predisposes them to future invasion of the system by the spirochetes. In the experimental animal it is very common to see a marked reaction at the point of inoculation and a total absence of generalized lesions. They have inoculated rabbits with syphilitic material in one testicle and excised the latter after the primary lesion had appeared and found that the incidence of generalized lesions had markedly increased and that these were present in nearly all animals. When they had excised the testicle forty-eight hours after the inoculation, thus producing a total suppression of the primary, all animals developed secondary lesions. Suppression of the primary lesion by drugs

sufficient to prevent its appearance, but not powerful enough to kill the spirochetes, gave the same results.

There are still men, well equipped to treat syphilis, who advocate the excision of the chancre when starting a course of the so-called abortive treatment. In the light of present knowledge, it would seem at best a useless procedure, when we consider the fact that systemic invasion occurs as early as forty-eight hours after infection and long before the chancre makes its appearance. The covering of the chancre with mercury ointment is quite a different matter. It has its usefulness in diminishing the infectiousness of the lesion and may reduce the possibility of spreading the disease.

As stated above, during the period between the chancre and the appearance of the secondary eruption, or, as it is sometimes called, the second period of incubation, invasion of the system by the spirochetes is going on. The latter may be found in the blood more commonly about forty days after the appearance of the primary lesion and in untreated cases may be found for six months. The presence of the organism in the blood in florid syphilis is not constant and the spirochetes are not numerous. The danger of infection by the blood is not great. Clinicians coming in contact with syphilitic blood are rarely, if ever, infected. The low infectivity of the blood may be due to an attenuation of the spirochetes in that location. Occasionally clinical evidence of visceral involvement is seen before the secondary rash makes its appearance. Chattelier and Bonnetterre<sup>10</sup> cite from the literature cases of preroseolar periostitis, arthritis, splenomegally, nephritis, precatious meningeal and cranial nerve involvement, phlebitis, one case of carotid thrombosis, and a preroseolar exanthem.

During treatment of the secondary stage of syphilis with arsphenamine, occasionally an intensification of the symptoms occurs. This is supposed to be due to the liberation of toxins by the lytic action of arsphenamine on the spirochetes. This process is called the Herxheimer reaction. The same phenomenon of intensification of the symptoms has been observed in the central nervous system and it is called neurorecidive or neurorecurrence. A negative Wassermann reaction in the blood of a syphilitic may become positive after arsphenamine treatment. This process is called a provocative Wassermann reaction. The same phenomenon is observed in the spinal fluid. A negative fluid may become positive in the Was-

Wassermann test and in albumin, globulin, cells, and the colloidal gold reaction; or a weakly positive fluid may become strongly positive. Gennerich<sup>87</sup> advanced the hypothesis that arsphenamine is capable of provoking spinal fluid changes in patients who have otherwise no central nervous system involvement. Finger<sup>88</sup> quotes from Gennerich that in untreated cases 59.5 per cent had positive spinal fluid findings, those treated with mercury and salvarsan had 84.7 per cent, and those treated with mercury alone had only 30 per cent of positive fluids. From the face of it, it becomes apparent that positive spinal fluid findings without clinical symptoms do not always mean neurosyphilis, because if it were otherwise the proportion of cases with central nervous system involvement would be much greater than it is at present. In this country, the available statistics are far from approaching the figures quoted above. As stated by Solomon and Klauder<sup>89</sup> there are a few cases that are made worse by treatment; the provocative reaction is not a frequent occurrence even in cases with definite symptoms of spinal involvement; there is no harm in treating these cases as they all finally get better from the treatment; all these conditions are so infrequent that they are only interesting from a theoretical standpoint and should cause no concern. In my own experience I observed only one case that developed neurosyphilis during the course of active antiluetic treatment out of a total of about two thousand patients treated with arsphenamine and mercury and not a single Herxheimer reaction was observed during the course of treatment of patients in the secondary stage of syphilis.

The treatment during that stage does not differ from the course pursued in primary lues, except that it must necessarily be stretched over a longer period. It is impossible to estimate the amount of treatment a patient should receive. It may be said, however, that if a patient has a negative Wassermann reaction after the first course of treatment, three or four more courses of arsphenamine and mercury according to the age of the disease should suffice, provided the reaction remains definitely negative during the entire period of treatment. The longer it takes to obtain a negative reaction on a patient, the longer should he be treated afterwards.

The greatest speculation and the greatest diversity of opinion on the subject of management and treatment is called forth by the cases of latent lues. There are still some who hold that a patient

who presents no symptoms of the disease, outside of a positive Wassermann reaction, should not be treated. The opinions upon which this contention is based are diametrically opposed to one another. Some hold that syphilis is incurable and the best that one can aspire to is the establishment of latency. Warthin<sup>90</sup> states that pathologically he never saw a cured case of syphilis. He found lesions in the liver, lungs, and other organs in most of the necropsies made on treated, cured (?), and undetermined cases of syphilis. The statement is significant, yet no conclusions can be drawn from it as it is too general, without any figures as to proportion or as to the kind and the amount of treatment received by these patients. Experiments conducted by Arzt and Kerl<sup>91</sup> are more elucidating. They were performed on three patients who received enough treatment to render their blood and spinal fluid negative to the Wassermann test and to all other serologic findings. These, as well as the clinical findings, were negative for a long time and in one case for eight years. Two of the patients developed erosions on the site of the chancre. Although spirochetes were not found in the secretion a successful inoculation of healthy animals by means of it was possible. The scar of the chancre in the third case was excised and spirochetes were found in the serum and in the stained tissues. The other view is that most of the patients with a positive reaction, but without clinical symptoms of the disease are actually cured only that the blood is so altered as to give a persistent positive Wassermann reaction. Crawford<sup>92</sup> says that a continued positive reaction in spite of treatment does not mean active lues. It may mean that immune bodies continue to be formed. Stokes and Busman<sup>93</sup> found 22 per cent of their latent, tertiary, and hereditary cases of syphilis with unchanged Wassermann reaction after treatment. Considering the fact that the last two of the three groups mentioned are the most refractory of all luetics to treatment, the proportion of poor results is extremely small when compared with a disease like tuberculosis. They state that it is not too wise to subject these cases to too long a treatment in order to change the reaction. When we consider the results of treatment of patients with latent lues, the above advice seems out of place. One group of forty-five latents under my care<sup>94</sup> were treated with courses consisting of five doses of 0.2 gm. each of arsphenamine and ten mercury injections at weekly intervals. Forty per cent of the patients

had a reversal of their reaction to the negative after the first course, 41 per cent after the second course, and 54 per cent were negative after the third course. A second group of patients<sup>1</sup> who were treated with larger doses ranging from four to six decigrams of arsphenamine gave 26.5 per cent negatives after the first course, 56 per cent after the second, and 66.6 per cent after the third course. Harmful effects from treatment with fifteen medium doses of arsphenamine stretched over a period of a whole year can hardly be expected, yet two thirds of the patients ended that period with a negative reaction. What is more interesting is the fact that fifteen injections of as small a dose as two decigrams of arsphenamine stretched over a period of about ten months resulted in a negative reaction in more than half of the cases. There are other reasons why a patient in that stage of the disease should be treated. Latency indicates a sort of balance between the defensive mechanism of the host and the virulence and aggressiveness of the germ. That balance can be upset or it can lose its equilibrium in consequence of certain factors as slight trauma or intervening disease, notably tuberculosis. In that manner, the patient finds himself, as it were, on a powder magazine. A third, and still more valid, reason is the ability of these patients to infect others. That latent luetics harbor spirochetes has been demonstrated. Engman and Eberson<sup>85</sup> found spirochetes in the inguinal glands in three out of fourteen cases of latent lues and, what is more important, they found the organisms in the semen in two out of seventeen specimens examined. Freuwald<sup>13</sup> found spirochetes in the lymph glands in ten per cent of patients with latent lues. That may explain the occurrence of active lesions after a long period of latency. Brown and Pearce<sup>95</sup> injected six rabbits with syphilitic material and three or more months after all lesions had subsided, they demonstrated spirochetes in the testicle. The spirochetes retained their virulence for other rabbits. Engman and Eberson<sup>85</sup> found negative results in the blood, in spinal fluids that gave a positive reaction to lues, and in nasal washings of patients with latent lues, while Savnick<sup>7</sup> found spirochetes in the mouth in five out of thirty-four latents.

Having established the fact that latent lues may infect, it is easy to imagine what a menace patients with that condition are to their families and to the public at large. The menace is still greater because a large proportion of these patients do not suspect any

trouble and are discovered accidentally as is the case when they apply for a food handler's certificate. The proportion of unsuspecting latents is comparatively large. Day and McNitt,<sup>96</sup> in a routine Wassermann examination of 2,925 patients clinically free from any signs of syphilis, found 15 per cent with a positive Wassermann reaction. Engman and Eberson<sup>85</sup> found that 15 per cent of theluetics treated at their clinic were true latent cases and express their conviction that the given number is far below the real average. They quote McNeill who made a study of 586 individuals among the southern negro and found 36 per cent with a positive Wassermann reaction. The detailed report is given in the tables below.

TABLE I

POSITIVE WASSERMANN REACTION IN APPARENTLY NORMAL INDIVIDUALS AND IN THOSE WITH DISEASE NOT DUE TO SYPHILIS

	NUMBER OF CASES	PER CENT OF POSITIVE WASSERMANN REACTIONS
Apparently normal adults	200	24
Children	52	95
Patients with pulmonary tuberculosis	60	23
typhoid fever	13	22
malaria	7	12
dysentery	12	20
pneumonia	30	30
pellagra	22	13
cancer	17	12
General average for the whole group		32%

TABLE II

POSITIVE WASSERMANN REACTION IN PATIENTS SUFFERING FROM CONDITIONS WHICH MAY BE CAUSED BY SYPHILIS

	NUMBER OF CASES	PER CENT OF POSITIVE WASSERMANN REACTIONS
Patients with arteriosclerosis	18	23
chronic interstitial nephritis	4	25
diffuse nephritis	60	48
paralysis	34	50
myocarditis	21	40
cirrhosis of the liver	6	60
bone and joint pains	30	80
General average for the whole group		49%

Out of one group of 998 cases of syphilis under my care<sup>94</sup> at Cornell Dispensary, there were 316 cases classed as latent. This proportion of over 30 per cent is perhaps a little too high as there

was included a small number of cases whose only complaint was headache, pain, etc., which properly do not belong in this class. Out of a second group of 375 cases<sup>1</sup> of syphilis, there were 57 latents or 15 per cent. This group was restricted to untreated cases without any signs of the disease at all. The only criterion for a diagnosis in these cases was the finding of a positive Wassermann reaction.

This brings us to the question of how reliable is the Wassermann reaction especially in latent cases without any luetic history. Practically all writers agree that a definitely positive reaction means syphilis invariably, while a negative reaction may mean nothing, because it is found in a certain number of active syphilitics. Lissner<sup>97</sup> says that too implicit a faith in the Wassermann reaction is driving us into an excess of treatment. He quotes Vile who says that to expect a negative reaction in a majority of cases is chasing shadows. That view is not corroborated by the results of treatment given above. As has been shown the Wassermann reaction is 100 per cent positive from the fifth week of the chancre on through the secondary stage. The percentage of positive reactions in the latent stage is not possible to estimate, as latents with negative reaction are not recognizable. In the tertiary period the reaction is positive in about 95 per cent of the cases, while in cerebrospinal lues it is positive only in 80 per cent of the cases. Larkin, Levy, and Fordyce<sup>98</sup> found 91 per cent negative reactions in cases of non-syphilitic skin diseases. Remembering the percentage of latent lues in apparently normal individuals, the figures given by the above authors appear to express the real state of affairs. The All-American Conference on Venereal Diseases in their preliminary report<sup>99</sup> say that a frank, reliable Wassermann reaction is evidence of lues with the following limitations. (1) In the absence of a luetic history and a positive reaction alone, the diagnosis should be made with great care and the test should be verified by another serologist. (2) A weak reaction cannot be accepted as diagnostic, but calls for further investigation. (3) A negative reaction cannot be regarded as proof of the absence of lues. (4) Cholesterinized antigen makes the test very sensitive and is of value in determining treatment. (5) A negative reaction is no indication for stopping treatment.

To determine the fact of cure, and to enhance the value of the Wassermann test, advantage is taken of the fact that a negative

reaction is sometimes made positive by treatment. This is called the provocative reaction. Three decigrams of arsphenamine ions injected intravenously and the blood is drawn for a Wassermann test on the three succeeding days following the injection. It is positive only in ten to twenty per cent of cases in which the test is performed. In addition to its provocative value, it has the advantage of a series of tests performed in succession and it has the merit of acting as an initial dose in a therapeutic test. A negative provocative, however, does not establish the fact of cure.

It is interesting to note that postmortem the Wassermann reaction is as effective as antemortem. Graves<sup>100</sup> proved it on a series of 400 postmortems. Lambert, Olmstead, and Stuart<sup>101</sup> at the Presbyterian Hospital found 85.7 per cent positive reactions on a series of twenty-three autopsies performed on patients who showed syphilitic changes during life. In another series of 188 cases with negative pathologic findings as to syphilis, none had a positive reaction.

Wassermann,<sup>102</sup> after recent experimental studies, admits a previous error, namely that the reaction is due to spirochetes or extracts of organs containing a large number of them. He states that the reaction is due to the production of antibodies against the lipoidal substances in the body which are produced as a result of the presence of spirochetes. Hence it is positive with all alcoholic extracts of animal organs containing lipoids. However, the value of the test is not diminished by these findings, it is positive in 90 per cent of the cases. In comparing the various modifications of the Wassermann test McIntire, North, and McIntire<sup>103</sup> state that the cholesterin antigen ice box fixation test is the first to be positive after the appearance of the initial lesion, the Hecht-Gradwohl modification is next, and the water-bath cholesterin antigen test is the last. The disappearance of the reaction after treatment occurs in reverse order.

The luetin test was brought out by Noguchi. Luetin is a sterile extract of spirochetes grown under anaerobic conditions. The reaction is due to an accumulation of particulate derivatives from dead spirochetes. A positive luetin reaction is evidenced by the appearance of a large inflamed papule twenty-four to forty-eight hours after an intradermal injection of 0.035 c.c. of luetin. It is surrounded by an area of erythema and it disappears within one



week. It may be vesicular or pustular. The test has now fallen out of use on account of grave defects in its administration. Strickler<sup>104</sup> showed that a repetition of the luetin test will give 21 per cent positive reactions in those that were negative with the original test. This is due to a cutaneous sensitization. Arsenic injected intravenously gives a positive luetin test in 51 per cent of non-luetic. Iodids and bromids taken during the time when the test is performed will yield a well marked reaction. Hannan<sup>105</sup> states that this state of affairs does not exist after mercury. Ward<sup>106</sup> states that the luetin test appears later than the Wassermann test during the course of the disease, but it persists longer; that it actually becomes negative after treatment and is a better gage as to cure than the latter; and therefore, when both tests are used together, they express a bigger truth than each separately.

In discussing primary and secondary lues, it was shown that the lesions disappear without leaving any trace of their former existence. The reason for it is that the amount of spirochetal toxins in the tissues determine the character of the lesions. According to Olson<sup>107</sup> the amount of toxins in the tissues in early lues is small, hence there is a complete tendency to resorption without necrosis. In late lesions, the amount is large, therefore there is degeneration and destruction of tissues. Healing always takes place by formation of scar tissue and there is permanent impairment of function of the organs involved proportional to the amount of destruction wrought. What can be accomplished with treatment is the checking of further progress of the disease and the resorption of infiltrations which have not yet gone on to complete necrosis. Once the latter has taken place, permanent injury is the result.

The characteristic lesion of tertiary lues is the gumma. Outside of lesions appearing on the skin and on accessible mucous membranes, tertiary lues has a great tendency to involve the viscera. When the lesions occur in the former location, the diagnosis is a comparatively simple matter. When there is visceral involvement without any external evidence of the disease, the matter is not so simple. Without entering into a discussion of visceral syphilis, it may be stated that syphilitic diseases of any organ can rarely be diagnosed by symptoms or physical signs. The Wassermann test is resorted to. In certain conditions as aortitis and aneurism in which the majority of instances are known to be due to syphilis, a positive reaction is

presumptive evidence of the presence of the disease. A patient, however, may have a chronic interstitial nephritis not due to syphilis and, at the same time, a positive reaction due to latent lues. Logically, one could reason that visceral disease and a positive Wassermann reaction in the same patient indicates syphilis, because, even if the disease of a certain organ has not originated as the result of spirochetal infection, the presence of the organisms in the body would lead, sooner or later, to the involvement of the diseased organ which becomes a point of least resistance to infection. This question can be decided only after the application of the therapeutic test. The diagnosis becomes further complicated by continually finding a negative reaction in about 5 per cent of patients with active tertiary lues. The provocative Wassermann reaction brings out only from 10 to 20 per cent of these cases. In the rest, the therapeutic test is the only means of making a diagnosis especially in the cases which Dreufus<sup>108</sup> termed masked syphilis. A number of these cases present definite lesions, but the latter cannot be distinguished from those due to other causes. Chronic, even acute arthritis, joint deformities, periostitis, exostoses, anal fissure, anemia, ozena, gastritis, etc., can be mentioned as examples. There are many cases, however, in which the signs of the disease are purely subjective. The commonest single symptom of masked syphilis is pain of a varied character and referred to various regions of the body as headaches, backache, joint, muscular, gastric, and precordial pain. Other vague and indefinite signs of syphilis are weakness, debility, nervousness, indigestion, etc. In fact, syphilis may resemble any disease on the calendar with the possible exception of the acute infectious diseases. How shall all these cases be diagnosed? The only way to detect the majority of them is by means of the routine Wassermann test. In a previous paper it was shown that with the establishment of the Wassermann test as a routine measure in the internal medicine department at Cornell the number of syphilitics with pain as a sole symptom rose from  $2\frac{1}{2}$  to  $12\frac{1}{2}$  per cent.

Although clinically it is not difficult to obtain satisfactory results, a reversion of the Wassermann reaction to the negative in tertiary lues is not accomplished with the same ease as in other stages of the disease. When a reversion of the reaction does occur, it is only after prolonged treatment. Besides, there is always the possibility

for the reaction to become positive again, even while the patient is under treatment. In a series of twenty-nine cases of active tertiary lues<sup>1</sup> only 10 per cent had a reversion to the negative after the first course of treatment, 23 per cent after the second, and 40 per cent after the third. In a number of them the reaction became positive again during treatment. It is interesting to note that tertiary syphilites without any definite lesions and in whom subjective symptoms were the only evidence of the disease, reacted to treatment very favorably. In a group of fourteen patients<sup>1</sup> the reaction became negative in 14 per cent after the first course of treatment, in 55.5 per cent after the second course, in 60 per cent after the third course, and in 100 per cent after the fourth course.

In treating tertiary lues, one must not forget that the prospect of eliminating every spirocheta diminishes with the duration of the disease, hence massive doses are not called for. Small doses should be given at long intervals and the patient must frequently have a complete rest from both the arsphenamine and the mercury treatment. Late syphilis occurs in older individuals who are not good subjects for intensive treatment. Several dangers must be guarded against. It is now a well established fact that patients with optic neuritis, auditory deafness, cardiac disease, aortitis, and aneurism cannot be restored, but injury to the patient may result from overdoses or from prolonged treatment. A large dose of arsphenamine may flare up a quiescent lesion and if the latter is located in an important organ, as the heart or aorta, severe damage may be the result. If a reaction is set up in a quiescent laryngeal ulcer, edema of the glottis may be the cause of death of the patient. Foci of septic infection, tuberculosis, cystitis, and pyelonephritis diminish the tolerance of the patient for arsenic. Influenza and bronchitis may turn to pneumonia after a Herxheimer reaction. Patients who had dermatoses before the treatment may develop exfoliative erythroderma if great caution is not exercised. In diseases of the kidney, arsphenamine is preferable to mercury. In vascular, myocardial, and in hepatic diseases, arsphenamine should be used very cautiously. Experience, however, teaches us that if used with great care beneficial results may be had from its employment.

A number of patients never get a reversal of their Wassermann reaction. Many discontinue treatment before a negative reaction could be expected, even under the most favorable conditions. In

a number of others, the reaction remains positive even after prolonged treatment. Bearing this in mind, there is the uncertainty of how to advise these patients as regards marriage. In a report to the French Society of Dermatology and Syphilis by its Committee on Marriage of Syphilitics<sup>109</sup> it is advised to allow a luetic with an irreducible blood serum, but with negative spinal fluid findings, to marry after five years of treatment. For women, additional courses of treatment are urged during pregnancies. In primary lues, if treatment is commenced before the Wassermann reaction becomes negative, it is advised to give the patient one year of treatment and to keep him under observation for a period of another year. After the appearance of the positive reaction or in the presence of secondaries, the patient is to receive two years of intensive treatment and should be kept for two more years under observation, before he is allowed to marry. Goubeau, disagreeing with the majority report, says that X plus three years should be the treatment, X representing the time that it takes all symptoms to clear up including the Wassermann reaction. Having seen a number of patients with secondary lues from whom a negative reaction was obtained after the first course of treatment and whose serum remained negative for five years or more after they had received treatment for a period of only one year, Goubeau's fears appear to be unfounded. The committee report goes on to say that if the spinal fluid gives a positive reaction in spite of treatment or if symptoms of involvement of the central nervous system are present, marriage is contraindicated. Old luetics who are negative clinically and serologically and who do not remember the date of their infection should be treated for a period of one year before they are allowed to marry. As many latents with a negative reaction revert to the positive after treatment I would amplify the above by saying that the reaction must remain negative throughout that period.

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## A CASE OF SYPHILIS OF THE INTESTINE

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(Received for publication, December 19, 1921)

CLINICAL symptoms of syphilis of the intestine are among the rarer manifestations of the disease; Wile<sup>1</sup> states that in a period of five years' observation of hospitalized syphilitic patients, he has never seen a case. He quotes Oberndorfer<sup>2</sup> who, up to 1900, had collected only twenty-four authentic cases from the literature. Since that time several more have been reported but the total number is yet so small, that the rarity of the condition and particularly, of its diagnosis during life, are deemed excuse enough for the presentation of the following case report, on which a presumptive diagnosis of syphilitic enteritis was made:

A. Y., male, white, oiler, married, aged fifty-one years. His family history was negative. *Marital History*.—His wife apparently is well but has had no children, the only two pregnancies resulting in miscarriages. *Personal History*.—Patient has always lived in Canada. Previous to the onset of present illness he has been well, except for an attack of gonorrhea thirty years ago, of which there has been no recurrence, and an extragenital sore, which was contracted the year before the gonorrheal infection. The sore was treated locally and healed in a short period of time. Sixteen years later he developed ulcers on his legs and a rash on his arms. For this condition he received some medicine, presumably mercury, which caused the disappearance of the lesions in a little while. His ordinary weight has been 160 pounds.

*History of the Present Illness*.—In the autumn of 1919 he commenced to have diarrhea, chiefly at night. The stools were liquid and contained a great deal of mucus and pus, but never any blood. The diarrhea increased in severity, till he was having from ten to twelve stools in the twenty-four hours. He complained of generalized abdominal pain and tenderness, urinary frequency, diurnal and nocturnal, and aching pains in the legs. He was losing weight steadily. He consulted several physicians and a complete gastric content and fecal examination was made, apparently with negative results. Several abdominal x-rays also were negative, as were the two serum Wassermanns. The condition was diagnosed as nervous diarrhea, but treatment of various kinds was without avail. The symptoms becoming steadily worse he was referred for diagnosis on March 30, 1921.

*Physical Examination*.—Patient was an emaciated, extremely cachectic man,

who looked very ill. There was slight icterus of the conjunctivæ and mucous membranes. *Skin*.—Situating just above the pubis there was a pigmented, non-indurated scar, the size of a twenty-five cent piece, and on the lateral surfaces of both legs, immediately above lateral malleoli, there were brownish pigmented scars, which had the appearance of healed rupial lesions. Otherwise, the skin was normal. *Mucous Membranes*.—The tongue showed marked leucoplakia with an exaggeration of the normal fissuring. There was considerable leucoplakia of the buccal mucous membrane at the oral angles. Sigmoidoscopic examination revealed some shallow ulcerations in the rectum. *Glands*.—There was general adenopathy, which was very suggestive of syphilis.

*Heart*.—Normal, superficial arteries showed slight sclerosis. *Pulse*.—Normal, temperature normal; respirations normal. *Lungs*.—Normal. *Abdominal Examination*.—Negative. *Reflexes*.—Normal; Pupils normal. *Weight*.—129 pounds. *Urinalysis*.—Dark amber, 1022, acid, albumin negative, sugar negative. *Fecal examination*.—Watery stool, grayish in color, containing quantities of mucus and pus but no blood. *Serum*.—Wassermann negative. Lumbar puncture refused. Mentally, patient showed lack of attention, defective memory, for both recent and long past events, and a negativistic attitude, which made any co-operation extremely difficult to secure.

He refused to have his wife examined.

The conclusion deduced from the *status praesens* of this patient was that the diagnosis, in all probability, rested among four conditions; i. e., amebic infestation of the intestine, intestinal tuberculosis, intestinal carcinoma, and intestinal syphilis.

The life-long residence of the patient in Canada rendered the first condition very unlikely.

Primary tuberculosis of the intestinal tract is rare in adults and particularly so in one in the fifth decade of life. Furthermore, in a case as long standing as this, one would expect a pneumonic involvement to be present. The absence of physical signs of tubercular invasion of the lungs also would exclude a secondary invasion of the intestine. From these considerations and the patient's persistently normal pulse, temperature, and respirations, it was decided that a tubercular etiology could be dismissed as a very improbable factor in the causation of the entity.

Malignant disease of the intestine usually manifests itself by alternating diarrhea and constipation, rather than by persistent diarrhea. With the time interval that had elapsed since the onset of symptoms a palpable tumor generally would be present, and this would be the more likely considering the steady progression of the disease which the patient presented.

The history of an extragenital sore and subsequent skin lesions, healing under mercury, the history of the wife having only two pregnancies, both terminating in miscarriages, and the physical findings of the scarring due to the former lesions, the leucoplakia, and fissuring of the lingual and buccal mucous membranes, the general adenopathy, and the rectal ulcerations were strongly confirmative of a diagnosis of syphilis, so, despite the negative serum Wassermann reaction it was decided to invoke the aid of the therapeutic test before more radical measures were instituted.

In order that a severe Herxheimer reaction might not be induced by commencing arsphenamine at once, on March 30, he was placed on hydrarg. cum cretæ, gr. i, t. i. d. and potassium iodide, gr. xv, t. i. d. for one week. There was no improvement at his next visit, on April 6, nevertheless he was given 0.45 gm. novarsenobillon, intravenously and the mercury by mouth continued. April 13, he reported that the diarrhea had diminished greatly, having had no movement at all in the last twenty-four hours. He was given 0.6 novarsenobillon intravenously and mercury by mouth as before. April 20. During the last week he has had only one movement daily and the motion was formed for the first time in over a year. The mucopus has diminished greatly. Treatment, 0.6 novarsenobillon, intravenously and mercury as before.

April 27. Patient's bowels have been moving regularly once daily. The soreness and pain in the abdomen have disappeared. His memory is improving. The frequency is much less. He complains of aching pains in extremities, probably due to the mercury. He has gained 10 pounds. Treatment, 0.6 gm. novarsenobillon, intravenously. On account of the pains the mercury was omitted for one week. May 4. The pains in extremities are less. He has had no diarrhea. Treatment, 0.6 gm. novarsenobillon, intravenously and mercury as before. May 11. Weight 142 lbs. Treatment, 0.6 gm. novarsenobillon, intravenously and mercury as before. May 18. Treatment, 0.6 gm. novarsenobillon, intravenously and mercury as before. May 25. Commencing on the 22nd, the diarrhea had returned, his bowels moving three times that day, four times on the 23rd, five times on the 24th. In spite of this, his weight has increased to 147 lbs. As the weather, at this time, had been exceedingly hot and the patient had been consuming large quantities of corn, it was felt that this apparent relapse was not an exacerbation of his disease but a concomitant acute intestinal derangement due to his diet. He was placed on pil. hydrarg. protoiodid gr.  $\frac{1}{4}$  t. i. d.

June 8. He has had no further diarrhea. The pil. protoiodid was continued.

July 6. Weight 152 lbs. There has been no recurrence of the diarrhea. His memory has improved greatly.

Aug. 12. His condition is good. He was given two weeks' interval off treatment and then the pil. protoiodid recommenced.

Sept. 26. Weight 157 lbs. He was given another two weeks' interval off treatment and then pil. protoiodid for four weeks.

Nov. 15. One would hardly recognize this patient. His icterus and cachectic pallor have disappeared entirely. He is no longer emaciated. His weight is 158 lbs. He has no recurrence of the diarrhea. The rectal ulcerations have healed completely. He is able to do a hard day's work and can eat anything. He is troubled still with frequency, having to rise twice nightly to void.

The course of this patient's condition under antisyphilitic treatment would seem to justify the diagnosis of syphilitic enteritis. Of course, it is impossible to do more than theorize as to the type and location of the lesion, but the symptoms, abdominal pain, diarrhea, mucus and pus in the stool, mild icterus, gradual emaciation and cachexia, are very suggestive of multiple ulcerating gummata of the colon.

#### CONCLUSIONS

1. A case is presented with a suggestive syphilitic history, showing symptoms of generalized abdominal pain and tenderness, severe diarrhea, with the passage of liquid stools, containing mucus and pus, mild icterus, gradual emaciation, and cachexia, failing memory, and a persistently negative serum Wassermann.

2. Recovery was rapid and complete, as far as concerns symptoms, under antisyphilitic treatment, substantiating a presumptive diagnosis of syphilitic enteritis.

3. While the many deficiencies from the standpoint of a scientific investigation of this case, due to the negativistic refusal of the patient to cooperate, are realized, it is believed that the rarity of the recognition of this condition during life and its arrest by antisyphilitic treatment warrant the publication of this case history.

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## THE VALUE OF NEUROLOGICAL EXAMINATION IN SYPHILIS\*

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(Received for publication, January 15, 1922)

WHENEVER the treatment of syphilis is undertaken, responsibility for the disease in all its forms is assumed; for no matter what part of the body is seemingly involved, therapy is neither successful nor complete unless the activity of *all* foci of infection has been terminated before permanent loss of function or deformity, has occurred. In the event of any one of these foci of infection having become inaccessible to available methods of sterilization, its activity, obviously, is beyond therapeutic control; or, if the treatment of accessible processes is not undertaken until after they have caused irreparable tissue destruction, the effects of this destruction will persist, although the disease process itself may have been terminated. These adverse contingencies are seldom allowed to arise in general syphilis, owing to the fact, that the disease, being systematically sought in all cases in which there is the least doubt as to diagnosis, is usually recognized while it is still within the limits of therapeutic controllability. In neurosyphilis, however, as these diagnostic precautions are not so universally taken, this form of the disease frequently remains unrecognized until its underlying lesions have become inaccessible to all methods of therapy, or until so much tissue destruction has taken place, as to render clinical recovery out of the question.

It is now realized that active neurosyphilis in an insidious form, may be present in any case in which the diagnosis of syphilis has been established, and that many forms of the disease, which are controllable at first, later become uncontrollable. Thus to allow neurosyphilis to pass through a curable, into an incurable phase, without having been sought, is an error of the most serious import—serious

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\*Read before the November (1921) semiannual open meeting of the Clinical Society of the New York Skin and Cancer Hospital.

to the patient because it often condemns him unnecessarily to permanent incapacity, and serious to the clinician, because such incapacity might have been anticipated and might have been prevented. As such a catastrophe is liable to occur in any case in which syphilis is known to exist, the essentiality of anticipating this occurrence by *seeking* the disease as a routine procedure in all cases of syphilis, seems obvious.

The frequent failure to take this routine diagnostic precaution, is due, apparently, to the tendency to regard neurosyphilis (as it was formerly) as a disease separate and distinct from general syphilis. This point of view, in the light of modern knowledge, however, is no longer justifiable. Involvement of the nervous system is not a *complication*, but like syphilis of the throat, or skin, it is merely one of the incidents which may occur in any case of treponemal infection, and which, having occurred, then pursues the pathologic course characteristic of syphilitic processes in general.

To detect neurosyphilis during its early or formative stages a *complete* neurologic and serologic examination is essential. The necessity of such a complete investigation is due to the fact that the disease process may occur in *any* part of the nervous system, and thus produce *any* symptom—functional or biochemical. The methods of examination generally employed in neurosyphilis overlook this fact, and are open to the criticism of being incomplete. Thus a clinical examination, which is limited to the search for the “classical signs” of tabes, paresis, and cerebrospinal syphilis, seeks evidence only of *localized* involvement of the nervous system—which evidence in tabes and paresis does not assume a typical form, until advanced parenchymatous degeneration has taken place. Hence to conclude (as is sometimes done) that neurosyphilis is asymptomatic, merely because the signs of certain advanced localized forms of the disease cannot be demonstrated, is obviously erroneous.

In like manner spinal fluid serology is limited both as to its interpretative and diagnostic value. When “positive” it indicates that neurosyphilis is present; but it does not determine which part of the nervous system is involved, nor whether the process is diffuse or circumscribed, single or multiple. Yet such precise knowledge is essential in the diagnosis of neurosyphilis; for the symptomatology and clinical course of neurosyphilis, depends not so much upon the

disease itself as upon the part of the nervous system which it happens to involve, and the decision as to the advisability of intravenous, intraspinal, or the combined method of treatment, again depends upon knowledge of the location of the lesion and its relative accessibility to one or the other of these methods of therapy. The positive spinal fluid Wassermann reaction appears (presumably at least) only when those lesions which are in the "Wassermann producing stage," are in communication with the cerebrospinal fluid of the spinal subarachnoid space; therefore when this reaction is "negative" it excludes only the existence of lesions in this pathologic or anatomic status, and cannot be regarded as proof of the fact that neurosyphilis is absent.\*

In a complete neurologic examination therefore, all functions of the nervous system, accessible to demonstration, must be tested. These tests may be generalized as follows:

1. An objective examination of all functions of sensibility (both general and special), followed by an inquiry as to present and past subjective sensory disturbances.

2. An objective examination of the various forms of motility (both of the appendicular musculature, and of the musculature of such special mechanisms as the eyes, jaws, face, tongue, pharynx, and head), followed by an inquiry as to present and past subjective motor disturbances.

3. An inquiry (and examination so far as it is possible) as to the functional status of the involuntary mechanisms—the vasomotor, the gastrointestinal, the genitourinary, and secretory systems.

4. An objective examination of the special functions of the cerebral cortex (stereognosis, speech, praxis, etc.), followed by an inquiry as to such organic disturbances as convulsions, loss of consciousness, etc., and as to such psychic disturbances as are characteristic of the neuroses, psychoses, and borderline states.

5. An objective examination of the kinesthetic function, namely the reaction of the nervous system to labyrinthine stimulation as induced by rotatory movement.

As a result of this method of examination, routinely employed, many cases of hitherto unsuspected neurosyphilis, with symptoms characteristic of the disease are revealed. Cases of this type,

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\*Solomon, H. C., and Klauder, J. V.: Neurosyphilis with Negative Spinal Fluid, Jour. Am. Med. Assn., lxxvii, No. 22, p. 1701.

however, are relatively few in proportion with another group in which abnormalities of nerve function *not* characteristic of neurosyphilis, are demonstrable. Thus one patient, who had been infected less than a year previously, complained of suboccipital headaches. His examination showed that the sense of pain (as induced by pricking the skin with a sharp-pointed object) was markedly diminished over the face and scalp, that the left pupil was dilated, and that the jaw reflexes were absent. Findings such as these, obviously, are not characteristic of neurosyphilis, nor is it generally regarded as the rule to be able to demonstrate neurosyphilis clinically, so soon after the primary infection. Yet in this case, the unquestionable fact remained that abnormalities of nerve function were found in conjunction with a disease especially prone to involve the nervous system. The question then arose as to how to prove or disprove the cause and effect relationship between these two occurrences. As a spinal fluid examination, which was then made, showed a strongly positive Wassermann reaction, this relationship seemed to have been established. This conclusion was further substantiated, when it was subsequently observed, that the sensation over the involved areas and the dilated pupil, returned to normal, and that the intensity of the spinal fluid Wassermann reaction became markedly lessened, as the result of combined intravenous and intraspinal treatment.

In another case, examined before the initial lesion had disappeared, the sense of pain was diminished over the face and lower part of the neck. No other neurologic symptoms were demonstrable, and both the spinal fluid Wassermann and globulin reactions were negative. In this case also, there was the association of neurofunctional abnormalities with a disease liable to involve the nervous system, but here the cause and effect relationship was not so apparent, owing to the negative nature of spinal fluid serology. The diagnosis of this case was at first held in abeyance, but when, after a few weeks' intravenous treatment, it was observed that the sensory disturbances had returned to normal, their neurosyphilitic origin seemed proved.

The bizarre and heterogeneous nature of the early symptoms of neurosyphilis, may be illustrated by citing, briefly, the findings in a few cases—all of which showed positive spinal fluid Wassermann reactions.



CASE A. showed a diminished sense of heat, and light touch, over the feet and ankles.

CASE B. showed double facial paralysis (of the peripheral type), questionably absent jaw and pectoral reflexes, and sluggish bicipital reflexes.

CASE C. showed diminution of all forms of superficial sensibility over the posterior thorax and lower third of the legs, atrophy of the left thenar eminence and of the extensor muscles of the right thumb.

CASE D. showed nystagmus upon looking upwards, to the right or to the left; vertigo of the falling type could not be induced by rotation, although the motor responses were normal.

IN CASE E. the outline of the right optic disc was not clear, the direct pupillary light reflex of the right eye and the consensual reflex of the left eye were sluggish; the deep reflexes could be elicited only upon reenforcement.

IN CASE F. the deep reflexes could be elicited only upon reenforcement; postrotatory vertigo could not be induced by rotation, and there was the subjective complaint of drowsiness.

IN CASE G. vertigo of the falling type could not be induced by rotation, although the motor responses were normal. A transitory epileptic coma occurred while spinal puncture was being made.

A list of cases illustrative of almost every abnormality of nerve function might be cited. Sometimes these abnormalities occur (as above) as isolated symptoms in patients in whom the spinal fluid Wassermann reaction is positive; sometimes they are found in conjunction with other abnormalities definitely characteristic of the neurosyphilitic syndromes; and sometimes they are observed in individuals in whom the blood Wassermann is positive, but in whom the spinal fluid is normal.

The necessity of regarding these atypical abnormalities (no matter how trivial they, in themselves, may seem) is illustrated by the following case:

The patient (who had been infected several years previously, and who had received irregular treatment), suddenly developed marked constipation, and, upon inquiry, it was also learned that there was a coincident infrequency of urination. A few weeks later, he became incontinent, both of the rectum and bladder, and impotent. Following this, spastic paraplegia appeared. Examination (which

was not made until the appearance of the paralysis) showed, the hypertonia and reflex changes characteristic of spastic paralysis; the absence of light touch over the scrotum, of the sense of pain over the midsacral region, of the ability to differentiate between heat and cold over the legs, of the sense of movement in the left great toe; a diminished sense of pressure on the legs, and a normal sense of vibration. The blood and spinal fluid Wassermann reactions were strongly positive. Under combined intraspinal and intravenous treatment, the sensory abnormalities disappeared, the bladder and rectum became normal, and the paralysis ceased to cause incapacity, although the signs of spasticity were still demonstrable.

Had this patient been examined routinely, the involvement of the nervous system would have been recognized during its incipient stages, and had treatment been instituted at that time, the paralysis and visceral symptoms would have been prevented. Yet, had this been done, the abnormalities observed would have corresponded to the atypical findings of the cases quoted above. Constipation would have been the one subjective symptom, and had this complaint been followed by a complete examination, infrequency of urination, and possibly a few indefinite sensory changes would have been the only abnormalities observed. Observed at the time of their occurrence, the importance of these atypical abnormalities, would have been questioned; yet regarded retrospectively, their definite relationship to an underlying neurosyphilitic process seems obvious.

In our own experience, the occurrence of neurofunctional abnormalities has been far more frequent than that of serologic abnormalities, and on this account we regard complete neurologic examinations at repeated intervals in syphilis, not only as important, but as imperative.

The interpretation of these atypical findings, their prognostic and therapeutic value, their relationship with such secondary serologic findings, as the cell count, the globulin, and colloidal gold reactions, form special problems, which cannot be discussed herein.

In the present discussion we have endeavored to show that the asymptomatic nature of neurosyphilis is not so frequent as is commonly believed. Neurosyphilis, even in the early stages is nearly always symptomatic, but as these symptoms are more frequently than not, atypical, they are not revealed by the conventional clin-

ical methods of examination. They are revealed, however, by complete, unprejudiced, examinations which test routinely, all functions of the nervous system; such methods of examination often demonstrate the existence of neurosyphilis in cases in which spinal fluid serology fails. The atypical nature of the findings elicited, however, questions the correctness of regarding them as expressions of an underlying neurosyphilitic process. Although there is much evidence in favor of this conclusion, and very little against it: First, the diagnosis of syphilis proves the existence of a disease especially prone to involve the nervous system; thus when neurofunctional abnormalities are found in individuals who are syphilitic—and otherwise normal—the neurosyphilitic origin of these abnormalities is highly probable. Second, neurofunctional findings which, occurring alone, are atypical, are often found in frank cases of neurosyphilis—sometimes as concomitant findings, and sometimes as early symptoms. Third, atypical neurofunctional abnormalities are often found in individuals in whom the spinal fluid Wassermann reactions are positive. Fourth, the syphilitic origin of atypical neurofunctional abnormalities is often proved by the therapeutic test, namely, their disappearance under antisyphilitic treatment. Fifth, the therapeutic test also proves the neurosyphilitic origin of atypical findings in cases in which the spinal fluid is normal.

We have also endeavored to emphasize the fact that neurosyphilis is not a complication of syphilis, but an incident which is liable to occur in any case of treponemal infection. The danger of this "incident" lies in its liability to become inaccessible to treatment, or to produce irreparable loss of function, before treatment is instituted. On account of these liabilities, and on account of the insidious nature of neurosyphilis, systematic search for the disease is prerequisite to successful therapy. To be efficient this search must be thorough, complete, and must be instituted at regular intervals. To demonstrate early neurosyphilis, by seeking only the signs of late neurosyphilis (as is often done) is an obvious absurdity. The one method of procedure which will detect early neurosyphilis, is that which tests, routinely, all functions of the nervous system, and all chemical reactions in the cerebrospinal fluid.

## ANOTHER TECHNIC FOR THE WASSERMANN TEST

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(Received for publication, January 3, 1921)

A METHOD of performing the Wassermann test in which the technic varies somewhat from the usual procedure has been in use at the Laboratory of Hygiene of the Vermont State Board of Health for several years, and seems well adapted at least to the small laboratory where comparatively few tests are made and where one person must do most or all of the work. The test has been made at the Vermont laboratory since 1912 during which time the writer has prepared all reagents and made the tests practically without assistance. In starting the test the methods of Noguchi<sup>1</sup> were followed. Some modifications described by Craig<sup>2</sup> have been adopted, as well as some that are original as far as known. The present method has been used without any change for over a year, in over 3000 tests, and has given satisfaction to the laboratory and to the clinicians.

### REAGENTS

1. *Cell Suspension*.—Human red cells are used, a .5 per cent suspension of washed cells in saline. In accordance with observations of Williams<sup>3</sup> only cells of Group IV (Moss classification) are now used.

2. *Complement*.—The clear serum is drawn off from blood secured from guinea pigs by cardiac puncture and is used undiluted.

3. *Syphilitic Antigens*.—Two antigens are used, each being diluted with 9 parts of saline.

(1) The acetone-insoluble lipid antigen of Noguchi, prepared from human heart.

(2) Cholesterinized extract of human heart, alcoholic.

4. *Patient's Serum*.—This is obtained by puncture of a vein, must be clear and is heated to 56°C for 20 minutes.

5. *Amboceptor*.—Rabbits are immunized against human erythrocytes by four intravenous injections followed by two or more in-

jections intraperitoneally. When the serum titrates 800 or over the animal is bled from the ear or heart and the serum is dried on filter paper.

Titration of all reagents are made before use, nearly in accordance with the directions of Craig.

#### TECHNIC OF TEST

##### *Amboceptor Titration.*—

1. Put 4 c.c. cell suspension in test tube, (A).
2. To remainder of cell suspension to be used add complement, 1 c.c. for each 25 c.c. of cell suspension. Mix well.
3. To test tube (A) add 4 c.c. of this suspension with complement.

##### *Mix.*

4. Put 1 c.c. of this mixture in each of six or seven test tubes.
5. To these tubes add amboceptor in varying amounts, e.g.,  $1 \times 5$  mm.,  $2 \times 5$  mm.,  $3 \times 5$  mm., etc. Leave one tube without amboceptor as control.
6. Incubate 2 hours with frequent shaking. Least amount of amboceptor causing hemolysis is one unit.

##### *Test Proper.*—

Use three tubes in a row, front to back, for each specimen, the rear one being a control without antigen.

1. To each tube add 1 c.c. cell suspension with complement.
2. To each tube in front row add .1 c.c. of antigen (1), diluted with 9 parts saline.
3. To each tube in the middle row add antigen (2) in the same way.
4. To each of the three tubes in a set add the inactivated serum of the patient, .1 c.c.
5. Incubate one hour at  $37^{\circ}\text{C}$  in incubator.
6. To each tube add 2 units amboceptor and shake. Incubate with occasional shaking till controls in rear row are hemolyzed.

The advantages apparently derived from the technic described are as follows:

1. The combining of erythrocytes, saline and complement, decreases the number of pipetting operations.
2. Errors from inaccurate pipetting of small amounts of complement and of cell suspension are avoided, as well as errors from inaccurately graduated pipettes.

3. The relation between amount of cells and of complement is the same in all tubes.

4. The first incubation furnishes a control against any non-specific hemolysis. Such hemolysis has never occurred since using cells of Group IV only.

If large numbers of tests were being made, and especially if but one antigen were used, probably the antigen could also be added *en masse* to a portion of the cell suspension.

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## THE ABSOLUTE DIAGNOSIS OF PRIMARY SYPHILIS

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(Received for publication, February 27, 1922)

**W**ITHOUT attempting to belittle the clinical syphilology established by Ricord and Fournier, the fact remains that the only early and absolute diagnosis of syphilitic chancre must rest upon the demonstration of the treponema or of the typical tissue reaction to its presence. Topically, there are several groups of procedures available, of which the valuable dark-field method is only one.

1. The demonstration of the living organism by the dark-field. Serum obtained from the surface of the lesion, by puncture of its rim, or of a regional lymph gland.

2. Finding the spirochetes by stained smears of fresh secretions. India ink method and by Giemsa's stain.

3. Biopsy is valuable in finding the typical pathology or for identifying the germs by staining them in the tissues.

4. Culture by transplantation of a piece of tissue in horse serum.

5. The Wassermann test, especially in well developed cases.

6. Animal inoculation.

### THE DARK-FIELD METHOD

Thompson,<sup>1</sup> Klauder,<sup>2</sup> Abramowietz,<sup>3</sup> Lane,<sup>4</sup> and others have pointed out the value of the dark-field method as the most accurate, simple and quickest means of arriving at an early positive diagnosis of syphilis, while Hazen<sup>5</sup> and Stokes and Busman<sup>6</sup> have emphasized its worth in relation to other procedures in the general diagnosis of syphilis. The method itself is simple. The presenting lesion is cleaned by rubbing with a piece of gauze saturated in normal salt solution. Any blood is removed and the after-coming drop of serum caught on a cover-glass and placed on the slide. Cedar oil is placed on the top of the cover-glass and also the top of the dark-field substage illuminator. When a good light is obtained on the field, it is centered and the observer should now find an intense black background illuminated by minute dancing bodies and larger areas of

blood cells, pus and mucus. If there is not too much debris present, search should reveal the slender, active, glistening treponema with from 10 to 20 spirals and about the length of two red blood cells. Its motions are of diagnostic importance and on analysis are found to be of three principal kinds: a cork-screw motion, a side-to-side lashing, and a contraction and expansion on its long axis. If the sub-stage and platform are warmed by exposure to the electric lamp for a half hour before the examination is made, the organisms will be more active than when examined on a cold apparatus.

The beginner should use care in making a differentiation between the *Treponema pallidum* and certain saprophytic spirochetes, especially in the mouth. (*Microdentium* and *mucosum*.) However, if the appearance of the tightly coiled spirals, the length, delicacy and characteristic motility of the organism of syphilis are kept in mind, few mistakes should occur.

Since it is not unusual to find the suspected sore treated with antiseptics, several methods have been devised for securing serum by puncture of the rim of the lesion or a regional lymph gland. Rather than lose several days by waiting for the chemical agent to be removed, (by aid of salt water dressings, etc.) puncture should always be done. The area over the enlarged gland is painted with iodine, frozen with ethyl chloride, and the needle inserted until the gland moves with the needle. Schultz<sup>7</sup> has suggested that a small amount of physiologic salt solution be injected into the gland and reaspirated. The needle is swung through several arcs and as much of the fluid aspirated as possible. If there is much blood present, the serum may be mixed with an equal amount of distilled water and examined at once. The puncture method of obtaining serum should be more generally used as it is rapid, painless and protects against the finding of saprophytes.

#### EXAMINATION OF SMEARS OF FRESH SECRETIONS

At the best, the methods for examining smears by stains are inferior to the dark-field method, but, in isolated communities, it may be impossible to take advantage of the latter method. Goodman<sup>8</sup> has pointed out that the main objections to stained preparations are that the characteristic motility of the organism is lost, a surprisingly large number of artefacts occur, and that in the process of making a smear the spirals are so changed by osmotic pressure that



it is difficult to differentiate pathogenic from nonpathogenic spirochetes.

A modification of Burri's India ink method may be used by collecting a drop of secretion on the end of a slide, adding a drop of freshly centrifugalized India ink and, by means of another slide, making a thin smear as in the preparation of a blood film which is then dried and examined with the oil immersion lens.

There are many preparations recommended for staining the causative organism, among them Wright's, Jenner's and Goldhorn's stains and the collargol method, but the favorite method is by means of the Giemsa stain. The formula for the stain is as follows:

Azure II eosin	3 grams
Azure II	8 "
Glycerin (Merck c. p.)	250 "
Methyl alcohol (Kohlbaum)	250 "

A mixture is made up with water, so that for each c.c. there is one drop of stain added. To this one drop of potassium carbonate (1 to 1000) solution is added to each c.c. of the mixture.

A thin film is made on a chemically clean slide, dried in the air and fixed in absolute alcohol for fifteen minutes, then stained in the dilute stain for one hour. The slide is then washed with distilled water, dried and examined. The *Spirocheta pallidum* is usually colored a delicate rose-pink by this stain.

#### BIOPSY

Biopsy of suspicious lesions should be encouraged, as it will often clear up the diagnosis when it is impossible to demonstrate the live infecting organism. Gehrman<sup>9</sup> thinks this procedure is especially valuable. A tiny piece of tissue is removed from the edge of the lesion by means of circumcision, if possible, or by a sharp razor or cutaneous punch, and an ordinary stained preparation made. Examination of the specimen thus obtained should show the involvement of the cutaneous vessels by an endarteritis and a periarteritis with characteristic round-cell infiltration, the typical histologic picture produced by syphilis in every stage.

The method recently devised by Warthin and Starry<sup>10</sup> for staining spirochetes in the tissues has largely removed the objections to

the older Levaditi method in which a large amount of tissue was used and much time consumed. Their method is as follows:

"1. Tissue fixed in neutral formal (4 per cent) or alcohol for one to three days. Ordinary routine formal solution will do.

"2. Wash thoroughly in distilled water to remove all traces of formal.

"3. Imbed in paraffine (alcohol, xylol, paraffine).

"4. Cut and mount sections on cover-glasses with albumin fixative.

"5. Remove paraffine (xylol, alcohol, water).

"6. Place cover-glasses in a saturated solution of ferric alum, or a 4 per cent solution of ferrous ammonium sulphate. Keep in incubator one to two hours.

"7. Wash in distilled water.

"8. Rinse cover-glass and section in a 2 per cent silver nitrate solution. Cover section with another perfectly clean cover-glass, which has been rinsed in the silver solution. The cover-glass will be held together by capillary attraction. Place them carefully in the bottom of a bottle of silver nitrate solution. Bottle should be covered with black paper, corked tightly, and placed in incubator for three to twenty-four hours.

"9. After impregnation, pour off the silver nitrate solution and rinse in distilled water without removing cover-glasses from bottle. Pour water into bottle, shake gently a few times, and then pour off.

"10. Pour reducing substance (Pyrogallie acid, 4 grams, 40 per cent formal, 5 c.c., distilled water, 100 c.c.) into bottle. See that fluid passes between cover-glasses, by pressing upon cover-glass with glass rod, or by shaking. Reduction must occur uniformly over the section or brown lines will result. Reduction is usually instantaneous. Remove section after two or three minutes, wipe off any brown or black precipitate on the albumin fixative about the section with a cloth, taking care not to touch the section.

"11. Wash in distilled water.

"12. Absolute alcohol, xylol, balsam."

#### CULTURE

Baeslock and Keane<sup>11</sup> found that a growth of the *Treponema pallidum* occurs directly from small pieces of human tissue implanted in horse serum medium. Their method, briefly, is as follows:

Normal horse serum is diluted with sterile distilled water in the

proportion of 3:1. Test-tubes are filled within an inch of the top, rubber stoppers inserted, and heated in a water bath to 60° C. for one hour. The following two days the tubes are heated one hour at 70° C. each day, until the media becomes syrupy. A piece of tissue is removed and planted in about  $\frac{2}{3}$  of the tube length, the media being at body heat. The lips of the tube are heated until the surface boils, then the stoppers are replaced. The inoculated tubes are incubated for three to five days at 37° C. when a few drops of the medium are examined by the dark-field apparatus.

#### THE WASSERMANN TEST

The value of the Wassermann test in the primary stage of syphilis has been variously given by many investigators. However, they practically all agree that under ten days only a small percentage of positive tests will be found, while the strength of the reaction will increase as the chancre develops until the fifth week, when the serum will be found practically always positive. Thus Sequeira<sup>12</sup> loosely states the reaction was positive in 90 per cent of cases. Lloyd<sup>13</sup> gives 30 per cent positive under ten days and 100 per cent at the end of the fifth week; Marshall and Ffrench,<sup>14</sup> 80 per cent positive at the end of the fourth week; Craig<sup>15</sup> 27 per cent positive in the first week and 79.4 in the fifth week. However, Klauder<sup>2</sup> has shown in a striking manner that the presence of a positive serum reaction varies inversely with the positivity of the dark-field examination and that the latter was of more value in diagnosis than the Wassermann.

A routine Wassermann test should always be done, not only for diagnosis but as a gauge to systemic involvement. Unlike the blood reactions of the later stages, even a weak-positive in the presence of chancre should be given diagnostic weight, but the idea of waiting for a strongly positive reaction, like awaiting the secondaries, before making a diagnosis approaches malpractice and cannot be too strongly condemned.

#### ANIMAL INOCULATION

Of great value in the study of experimental syphilis, animal inoculation is of little practical worth in diagnosis for the reason that much time is lost between inoculation and the development of typical lesions. The technic is simple: two or three drops of serum

are taken up with a small hypodermic syringe; then, as Hazen<sup>16</sup> has suggested, mixed with normal salt solution, and injected, through the surgically prepared scrotum of a large rabbit, into the center of the testicle.

After an incubation of about two weeks, a gradual swelling takes place, due to the round-cell infiltration. In from four to six weeks the testicle will be of large size and the demonstration of treponema should be easy. Scrotal and corneal inoculations are made by slitting the organs and inserting a small piece of the lesion under investigation.

To summarize: the dark-field apparatus offers the procedure of choice in the early diagnosis of syphilis; stained smears are a poor substitute for this method and should be discouraged. Examinations of tissue from the suspected lesion should be more popular. The Wassermann reaction will be of value when the examination for the treponema is persistently negative. Culture and animal inoculation are of little practical worth in early diagnosis.

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## STUDIES IN THE STANDARDIZATION OF THE WASSERMANN REACTION. XXIV\*

### A COMPARATIVE STUDY OF TISSUE EXTRACTS (ANTIGENS) AND METHODS OF PREPARATION

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(Received for publication November 30, 1920)

**P**ROBABLY the most important single factor influencing the results and practical value of the complement-fixation test in syphilis concerns the kind of organ extract employed as "antigen." In our opinion the divergent Wassermann reactions observed in different laboratories with portions of the blood of the same person, have been due in large part to the difference in antigens employed, referable not only to a difference in kind, but to dosage as well.

In our attempts to standardize the complement-fixation test for syphilis, a decision on the kind of extract to employ has proved most difficult and has required a great deal of experimental study with many different kinds of extracts; likewise the technic for titrating or standardizing the extracts, which is the keynote of a uniform and standardized complement-fixation technic.

#### REVIEW OF LITERATURE

As is now well known the first "antigens" employed by Wassermann, Neisser and Bruck<sup>1</sup> and Detre,<sup>2</sup> were salt solution extracts of syphilitic tissues, pure cultures of *T. pallidum* not being available. With these extracts the reactions were considered biologically specific, that is, a fixation of complement by antibody and specific pallida antigen.

No one supposed that the mechanism was entirely different until Marie and Levaditi<sup>3</sup> and Landsteiner, Müller and Pötzl<sup>4</sup> showed that similar extracts of nonsyphilitic tissues and, indeed, alcoholic extracts of guinea pig heart, served equally well as "antigen" in the

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\*Investigation aided by funds accruing from the preparation of arsphenamine.

Wassermann test. This ushered in the second period of development of the Wassermann reaction, stimulating research activity and the publication of numerous papers confirming the observation that extracts of normal organs may be used as "antigen" and that the reaction was not biologically specific in the sense of Bordet-Gengou's phenomenon.

One result of these researches was to show that the real antigenic substances in both salt solution and alcoholic extracts of either syphilitic or normal tissues, were lipoidal bodies and much work was done on the identification of these by Levaditi and Yamanouchi,<sup>5</sup> Porges and Meier,<sup>6</sup> Sachs and Altman,<sup>7</sup> Fleischmann,<sup>8</sup> Noguchi,<sup>9</sup> Hessberg<sup>10</sup> and others. Without detailing the large amount of investigation on this subject, the net results showed that many lipoidal substances were concerned, that no one was as good as a mixture and that synthetic "antigens" were generally unsuccessful. Noguchi's work was continued for several years with the aid of Bronfenbrenner<sup>11</sup> and proved particularly fruitful, having resulted in the discovery that the phosphatids and particularly lecithins, were highly antigenic, a method being worked out for preparing these from tissues and now well known as the extracts of acetone insoluble lipoids.

While numerous researches had shown that alcoholic solutions of cholesterin were but feebly antigenic, Browning, Cruickshank and McKenzie<sup>12</sup> found that the addition of cholesterin to solutions of lecithins greatly improved their antigenic value; Sachs<sup>13</sup> found that the addition of cholesterin to alcoholic extracts of heart muscle greatly improved the antigenic value of such extracts, and these discoveries may be said to have ushered in a third epoch in the development of "antigens" for the Wassermann test. Sachs' work was quickly confirmed in England by McIntosh and Fieldes<sup>14</sup> and in this country by Walker and Swift<sup>15</sup> and Kolmer, Laubaugh and Williams.<sup>16</sup> These cholesterolized extracts have come into general use and are regarded by Field<sup>17</sup> and other serologists as approaching closest to the ideals of a standard antigen. As shown by Kolmer and his associates they may, however, under certain circumstances, yield a small percentage of weak falsely-positive reactions with the sera of nonsyphilitic persons; this finding has been confirmed by several serologists so that opinions differ regarding the practical value of these extracts, although all serologists appear to agree that they are the most sensitive of any of which we have knowledge.

TABLE I

TISSUE EXTRACTS EMPLOYED BY VARIOUS AUTHORS FOR "ANTIGEN" IN THE WASSERMANN TEST

AUTHORS	REFERENCE	EXTRACTS EMPLOYED
	TO BIBLIOGRAPHY	
Browning, Cruickshank and McKenzie	12	Lecithin and cholesterin
Sachs	13	Cholest. alc. extract heart
McIntosh and Fildes	14	Lecithin and cholesterin
Noguchi and Bronfenbrenner	11	Acetone insoluble lipoids
McRae, Eisenbrey and Swift	19	Acetone insoluble lipoids
Fitzgerald and Leathes	20	Acetone insoluble lipoids
Walker and Swift	15	Cholest. alcoholic extract heart
Field	17	Cholest. alcoholic extract heart
Walker	21	Cholest. alcoholic extract heart
Kolmer et al	16	3 including cholest. alcoholic heart
Thomas and Ivy	22	Plain alcoholic extract syphilitic liver
Thompson (Loyd)	23	Cholest. alcoholic extract heart
Boas	24	Plain alcoholic extract guinea pig heart
Citron and Garbat	25	Alcoholic extract guinea pig heart
Ottenberg	26	Plain and cholest. alcoholic extract heart
Craig	27	Cholest. alcoholic extract heart
Vedder	28	Cholest. alcoholic extract heart
MacNeal	29	Cholest. alcoholic extract heart
Judd	30	Cholest. alcoholic extract heart
Simon	31	Acetone insoluble lipoids
Kaplan	32	Cholest. alcoholic extract guinea pig heart
N. Y. Board of Health	33	Plain alcoholic extract guinea pig heart
Hopkins and Zimmerman	34	Cholest. alcoholic extract heart
Roderick	35	Cholest. alcoholic extract human heart
McClure	36	Plain alcoholic extract heart
Simonelli	37	Plain alcoholic extract rabbit cornea
Snow and Cooper	38	Plain extracts
Larkin	39	Plain and cholest. extracts
Smith and McNeal	40	Plain alcoholic extract heart
Desmonliere	41	Cholest. alcoholic extract human heart
Ecker and Sasano	42	Plain alcoholic extract beef heart
Varney and Baeslack	43	Plain alcoholic extract rabbit gumma
Ruediger	44	Plain alcoholic extract human and beef heart
Magnuson	45	Acetone insoluble lipoids
Coca and L'Esperance	46-47	Acetone insoluble lipoids
Owen and Martin	48	Plain alcoholic extract human heart
Neyman and Gager	49	Plain and cholesterolized; acet. insol. lipoids
Stillman	50	Cholesterolized alcoholic extract

In this connection it must be stated that the tendency to nonspecific reactions by cholesterolized extracts can be overcome and prevented by technical factors, and that they bid fair for acceptance as the best "antigens" for the Wassermann test.

At the present time the extracts generally employed may be grouped under four kinds, namely, (a) plain alcoholic extracts of syphilitic liver; (b) plain alcoholic extracts of normal tissues and particularly human, beef and guinea pig heart; (c) cholesterolized alcoholic extracts of normal tissues and (d) acetone insoluble lipoids of normal tissues. The use of plain alcoholic extracts has increased with the adoption of the "cold" method of primary incubation, as reviewed in a former paper of this series.<sup>18</sup> A review of recent literature on the subject of "antigens" employed in tests with heated serum and guinea pig complement, has been summarized in Table I to show the kind of extracts being used; in tests using unheated serum, Noguchi's acetone insoluble lipoids are mostly employed. The list is by no means complete and serologists may have changed their technic since the publication of papers referred to, but it is of value as showing the kinds of extracts employed and particularly how few adhere to alcoholic extracts of syphilitic liver and how cholesterolized extracts are gaining in popularity.

#### NOMENCLATURE

Certainly the phrase "specific antigen" cannot be applied to the extracts in common use; very probably salt solution extracts of syphilitic tissues (Wassermann's and Detre's original antigens) may contain specific products of pallida, but this is doubtful of alcoholic extracts. Following the successful cultivation of *T. pallidum*, Noguchi<sup>51</sup> prepared saline extracts and secured positive complement-fixation reactions with the sera of some luetic persons, but these antigens have not proved of practical value. Craig and Nichols<sup>52</sup> found that alcoholic extracts of *T. pallida* gave a large percentage of negative reactions with syphilitic sera; Kolmer, Williams and Laubaugh<sup>53</sup> found that both saline and alcoholic extracts were but feebly antigenic and particularly the latter, and that the reactions observed may be due to the extraction of sufficient lipoidal substances of nonspecific character from the microparasites.

The term "antigen" therefore is a misnomer as applied to the



extracts of tissues commonly employed; as shown by Seligmann and Pinkus,<sup>54</sup> Fitzgerald and Leathes<sup>20</sup> and others, they do not produce antibodies when injected into the lower animals. A better term is "extract," although "antigen" may be used for the purpose of convenience and will probably continue to be most widely used by reason of custom, but it should be clearly understood that the extracts commonly employed are not specific and not antigens in the real meaning of the word.

The phrases "antigenic sensitiveness" and "antigenic unit" may be still used however, because of their expressiveness and the difficulty of finding better terms, even though we are not dealing with real antigens in the Wassermann test as commonly conducted.

#### PROPERTIES OF ORGAN EXTRACTS

Salt solution and alcoholic extracts of tissues possess the following three well-known properties in relation to complement-fixation tests: hemolytic, anticomplementary and antigenic activities. Extracts vary greatly in these properties and the most desirable are those possessing high antigenic and low anticomplementary and hemolytic activity.

The investigations of Noguchi,<sup>9</sup> Erlandsen,<sup>55</sup> Neyman and Gager<sup>49</sup> and others, have indicated that the properties of various substances commonly found in alcoholic and ethereal extracts of wet tissues may be summarized as follows:

Proteins and cleavage products of proteins	} Slightly hemolytic Highly anticomplementary Slightly antigenic
Cholesterin and unidentified lipoidal bodies	
Various salts	
Soaps and neutral fats	} Highly hemolytic Slightly anticomplementary Slightly antigenic
Saturated and unsaturated fatty acids	
Bile salts (in extracts of liver)	
Phosphatids (especially lecithin); diaminomonophosphatids	} Slightly hemolytic Slightly anticomplementary Highly antigenic

#### THE IDEAL EXTRACT

1. It is apparent that extracts employed as antigens in the syphilis complement-fixation test should be as *highly antigenic and as little hemolytic and anticomplementary as possible*; the dose corresponding to four or five antigenic units should be at least ten times less the

anticomplementary and hemolytic units and especially with the refrigerator method of primary incubation, in order to conduct a sensitive test and yet remain free of the suspicion of yielding non-specific reactions. In other words, the antigenic unit should be at least forty times less than the anticomplementary and hemolytic units and especially if cholesterol has been added.

2. The extract should be *highly polytropic*; by this we mean it should possess affinity for the lipophilic antibodies in the sera of all syphilitics. One of us (Kolmer) as a result of routinely conducting the Wassermann test with three or more extracts for the past eight years, has frequently encountered sera containing an antibody with greater affinity for one extract than for others, all extracts being employed in a dose of two antigenic units. These results have been ascribed to the presence in a particular extract of a lipoidal substance having a peculiar or marked affinity for the lipodotropic antibody of a particular serum and the subject has not received the attention of other serologists warranted by its practical importance. *The addition of cholesterol to extracts renders them highly polytropic and constitutes one of the real values of cholesterolized extracts.*

3. The extract should *keep well* for several months at least; it is not uncommon for an extract to keep practically unchanged for a year or more while others may become highly anticomplementary in a week or month.

4. The process of making the extract should be so standardized that different extracts may possess approximately the same properties; any method yielding only occasionally an acceptable extract is not satisfactory.

Of course cheapness and simplicity of manufacture are likewise desirable features of any method, but these are certainly of much less importance; *quality must be recognized as of prime importance, as so much of the real value of the Wassermann test, namely, for the diagnosis of the obscure rather than the clinically manifest case of syphilis, depends upon the goodness of the extract employed as antigen.*

#### PURPOSES OF INVESTIGATION

The primary object of our investigation was a search for this ideal extract; owing to our imperfect knowledge of the nature of

the Wassermann test the search is like groping in the dark and was conducted by preparing and testing extracts after numerous methods described in the literature and subjecting all to close unbiased scrutiny and experimental trial. With this object in view we have applied our studies on subjects of fundamental interest as follows:

1. A comparative study of methods for the preparation of tissue extracts as follows: (a) alcohol versus salt solution extracts of tissues; (b) alcohol versus ether extracts; (c) 95 per cent versus absolute alcohol for extractions; (d) temperature in relation to alcoholic extraction; (e) time required for extraction with alcohol; (f) the relation of kind of tissue extracted to the properties of the extract; (g) the alcoholic extraction of dried versus wet tissues and (h) the influence of re-enforcing alcoholic extracts of tissues with cholesterin.

2. Comparative studies of the antigenic, anticomplementary and hemolytic properties of the four main kinds of extracts in common use, namely, plain alcoholic extracts of tissues, cholesterin re-enforced alcoholic extracts of tissues, acetone insoluble lipoids and mixtures of acetone insoluble lipoids (lecithins) and cholesterin.

The knowledge gained from a review of the literature giving the experiences and studies of others in addition to the information gained from the above work, have been utilized in building up an antigen of superior properties and described in a separate article;<sup>57</sup> likewise the results of our studies bearing upon the preservation and technic of titration of extracts are given elsewhere.<sup>56</sup>

## Part 1

### A STUDY OF METHODS FOR THE PREPARATION OF ORGAN EXTRACTS

*Alcohol Versus Salt Solution Extracts of Tissues.*—It has been stated but not proved, that salt solution extracts of syphilitic and nonsyphilitic tissues contain the same lipoidal substances as alcoholic extracts, although the quantities may be different. Saline extracts are apparently still used and especially in some European laboratories.

Comparative tests with saline and alcoholic extracts of the same tissues prepared at the same time and under identical conditions have proved for us that *alcohol serves the extraction of more antigenic substances than salt solution* regardless of the tissue employed

and the duration and temperature of extraction. The results of extractions of nonsyphilitic human heart and liver with alcohol and saline solution at 38° C. for two to twelve days are shown in Tables II and III as examples of a series of similar extractions of different tissues for periods varying from two to eleven days and at temperatures varying from 38, 22 and 6° C. The technic of titration to be described in detail in a later communication,<sup>56</sup> was identical in every particular for each extract.

As shown in Tables II and III and similar experiments, alcoholic

TABLE II

EXTRACTION OF HUMAN HEART WITH ALCOHOL VERSUS SALINE SOLUTION AT 38°C

EXTRACTION DAYS	ALCOHOL			SALINE SOLUTION		
	HEMOLYTIC 1:5	ANTICOMPLEM. 1:10	ANTIGENIC 0.1	HEMOLYTIC 1:5	ANTICOMPLEM. 1:10	ANTIGENIC 0.1
2	—*	—	—**	—	—	—**
4	0.5	—	1:10	—	—	—
8	0.5	—	1:10	—	—	—
12	0.5	0.5	1:20	—	—	—

\*Not hemolytic or anticomplementary in 0.5 c.c.

\*\*Not antigenic in 0.1 c.c. of 1:5 dilution.

TABLE III

EXTRACTION OF HUMAN LIVER (NORMAL) WITH ALCOHOL VERSUS SALINE SOLUTION AT 38°C.

EXTRACTION DAYS	ALCOHOL			SALINE SOLUTION		
	HEMOLYTIC 1:5	ANTICOMPLEM. 1:10	ANTIGENIC 0.1	HEMOLYTIC 1:5	ANTICOMPLEM. 1:10	ANTIGENIC 0.1
2	0.4	—*	—**	—	—	—**
4	0.4	—	1.5	—	—	—
8	0.2	0.4	1.5	—	—	—
12	0.2	0.4	1.5	—	—	—

\*Not hemolytic or anticomplementary in 0.5 c.c.

\*\*Not antigenic in 0.1 c.c. of 1:5 dilution.

TABLE IV

THE INFLUENCE OF TEMPERATURE UPON THE EXTRACTION OF BEEF HEART WITH 95 PER CENT ALCOHOL

EXTRACTION DAYS	INCUBATOR 38° C.			ROOM 22° C.			REFRIGERATOR 6° C.		
	HEMO. 1:5	ANTI-COMP. 1:10	ANTIGEN. 0.1	HEMO. 1:5	ANTI-COMP. 1:10	ANTIGEN. 0.1	HEMO. 1:5	ANTI-COMP. 1:10	ANTIGEN. 0.1
4	0.5	—*	1:10	0.5	—	1:10	—	—	1:10
8	0.5	—	1:10	0.5	—	1:10	—	—	1:10
11	0.5	0.5	1:20	0.5	0.5	1:10	—	0.5	1:10

\*Not anticomplementary in 0.5 c.c. of 1:10 dilution.

extracts were more antigenic and at the same time more hemolytic and anticomplementary than saline extracts. Those laboratories employing saline extracts usually follow Wassermann's custom of determining the anticomplementary unit and using one-half this amount for the main tests; but this principle and practice are wrong, inasmuch as there is no constant relation between anticomplementary and antigenic activities and an extract may be anticomplementary and yet almost devoid of antigenic sensitiveness.

*Alcohol Versus Ether Extractions.*—As previously stated the investigations of Neymann and Gager and others have shown that ether extracts from wet and dried tissues lipoidal substances which are not only anticomplementary and feebly antigenic but likewise highly hemolytic; Noguchi purified these ether extracts, that is, largely removed the anticomplementary and hemolytic substances, by precipitating with acetone and recovering the highly antigenic lecithins in the residue.

Our experiments, consisting of the extraction of similar amounts of wet and dried tissues and especially human and beef heart with ether and absolute ethyl alcohol under identical conditions, have usually shown that the *ether extracts were highly hemolytic* although the anticomplementary and antigenic values were usually similar to those of the alcoholic extracts; furthermore, alcohol usually extracted more lipoidal and other substances than ether, as determined by weighing the residues after evaporation.

Mixtures of alcohol and ether in equal parts did not serve better than alcohol alone for the extraction of wet and dried tissues.

*Ethereal extracts therefore, cannot be utilized for antigen because of their highly hemolytic properties; however, they usually contain large amounts of antigenic substances and principally lecithins, that may be removed from the crude ether extracts and utilized for antigen by precipitation with an excess of acetone.*

*Alcohol Versus Acetone Extraction.*—Kolle and Steiner<sup>55</sup> have advocated the extraction of dried tissues with acetone for antigen in the Wassermann test; Kolmer, Laubach, Casselman and Williams<sup>16</sup> have found acetone extracts of syphilitic liver somewhat inferior to alcoholic extracts.

In this study plain acetone extracts of wet and dried non-syphilitic human heart and liver and beef heart, have usually possessed antigenic activity but somewhat less than extracts prepared

with absolute ethyl alcohol under identical conditions; the anti-complementary and hemolytic activities of both kinds of extracts were usually quite similar.

*95 per cent, versus 99 + per cent, ethyl alcohol.*—Absolute ethyl alcohol is commonly used for the extraction of tissues, but owing to the increasing difficulty of securing high grade alcohol it is a matter of practical importance to ascertain if the usual 94-95 per cent may be utilized for the extractions of tissues.

In our experiments wet pastes of human, beef and guinea pig hearts were extracted with 95 per cent and "absolute" ethyl (highest grade) alcohols under identical conditions and at the same time; 10 grams of finely minced tissue were used with 100 c.c. of alcohol and the extractions conducted in an incubator at 38° C. for eight days with hemolytic, anticomplementary and antigenic titrations on the first, second, third, fourth and eighth days; the results are given in Tables VIII, IX, and X.

The results of these and additional experiments of a similar character employing dried human and beef heart muscle, have shown that extracts made with 95 per cent alcohol are quite similar in all properties to those made with "absolute" ethyl alcohol; the latter extracts were, however, occasionally slightly superior in antigenic activity, and for this reason "*absolute*" ethyl alcohol is to be preferred and especially for the extraction of wet tissues, but is not absolutely necessary for the preparation of extracts.

*Ethyl Versus Methyl Alcohol.*—Custom has sanctioned the use of ethyl alcohol for the extraction of tissues, but numerous experiments have shown that almost as good extracts are obtained with methyl alcohol providing dried tissues are employed. Curiously methyl alcohol extracts of wet tissues as fresh minced beef heart, were usually decidedly inferior in antigenic activity to ethyl alcohol extracts prepared at the same time and in the same manner. Our experiments were conducted with high purity absolute ethyl alcohol and acetone free methyl alcohol of highest purity obtainable. No differences were observed in the anticomplementary and hemolytic activities of extracts prepared with these alcohols. Either alcohol may be used successfully for the extraction of dried tissues but ethyl alcohol is better for the extraction of wet or fresh tissues.

*Temperature in Relation to Extraction of Tissues with Alcohol.*—Tissues are generally extracted in an incubator at 38° C.

Comparative experiments consisting of the extraction of non-syphilitic human heart and liver and beef heart with alcohol at 38° C. (incubator), 22° C. (room) and 6° C. (refrigerator) have shown that all are satisfactory; the results observed with extracts of wet beef heart titrated on the fourth, eighth and eleventh days are shown in Table IV.

Similar results have been observed with extracts of human heart and liver and indicate that *extraction of tissues with alcohol at temperatures varying from 6 to 38° C. yield antigens of similar properties; usually, however, extractions at 38° C. guarding against evaporation and adding alcohol to make up for the inevitable slight loss, have yielded extracts slightly superior in antigenic activity in a somewhat shorter period of time and for these reasons this temperature is to be preferred*, but is not absolutely necessary for the preparation of good extracts.

Ecker and Sasano<sup>42</sup> have recently described a method for the preparation of extracts in one to three hours with boiling alcohol; we tried this method with wet and dried beef heart before and after preliminary extraction with ether in a Soxhlet apparatus, but the extracts were unsatisfactory, owing to feeble antigenic activity.

*Time Required for the Extraction of Tissues with Alcohol.*—Tissues are usually extracted with alcohol at 38° C. for four to fourteen days, although some authors have advocated twelve hours and others several weeks.

In our experiments, wet and dried nonsyphilitic human heart and liver and beef heart have been extracted at 38° C. with 95 per cent and absolute ethyl alcohol for periods up to twenty-one days and titrated for hemolytic, anticomplementary and antigenic activity at frequent intervals.

The results of a few of these experiments are shown in Tables V, VI, VIII, IX and X.

In our experience hemolytic, anticomplementary and antigenic principles may be present in the alcohol on and after the first day of extraction, *but the extracts do not usually reach their maximum in antigenic activity until the fifth to eighth days; from the first to eighth days the extracts acquire slightly greater hemolytic and anticomplementary activity but especially gain in antigenic activity.* For these reasons we believe the extraction of wet and dried tissue

TABLE V

THE DURATION OF EXTRACTION WITH ALCOHOL AT 37° C. UPON THE ANTICOMPLEMENTARY AND ANTIGENIC ACTIVITY OF EXTRACTS OF HUMAN HEART AND LIVER.

DURATION	HEART EXTRACT		LIVER EXTRACT	
	ANTICOMPLEMENTARY 1:5	ANTIGENIC 1:20	ANTICOMPLEMENTARY 1:5	ANTIGENIC 1:20
1 day	0.8	—	0.9	—
5 days	0.8	—	0.9	—
8 days	0.8	0.4	0.9	—
14 days	0.5	0.3	0.6	0.4
21 days	0.3	0.3	0.4	0.3

TABLE VI

THE DURATION OF EXTRACTION WITH ALCOHOL AT 37° C. UPON THE ANTICOMPLEMENTARY AND ANTIGENIC ACTIVITY OF EXTRACTS OF GUINEA PIG HEART AND LIVER

DURATION	HEART EXTRACT		LIVER EXTRACT	
	ANTICOMPLEMENTARY 1:5	ANTIGENIC 1:20	ANTICOMPLEMENTARY 1:5	ANTIGENIC 1:20
1 day	0.7	—	1.0	—
5 days	0.6	—	1.0	—
8 days	0.6	0.4	1.0	0.5
14 days	0.5	0.3	0.9	0.4
21 days	0.5	0.3	0.7	0.4

with alcohol at 38° C. should be seven to eight days at least, nothing being gained by more prolonged extractions.

*The Relation of Kind of Tissue to the Properties of Organ Extracts.*—A large number of different tissues have been employed by various workers for the preparation of organ extracts; probably the most widely used are normal and syphilitic human liver, human, beef and guinea pig heart, beef liver and guinea pig liver and spleen. Simonelli has used syphilitic cornea of rabbit; Desmonliere beef tonsils and Baeslack syphilitic testes of rabbits, but none of these have been generally adopted.

Without entering into a discussion on the subject of specific antigen, it would appear that the majority of serologists have found extracts of nonsyphilitic tissues equal or superior to extracts of syphilitic liver as antigens for the Wassermann test; the only extracts which we believe can merit the designation of "specific" in the biological sense, are saline rather than alcoholic extracts of pure cultures of *T. pallida* or of tissues containing large numbers of



TABLE VII  
COMPARATIVE ANTICOMPLEMENTARY AND ANTIGENIC ACTIVITY OF EXTRACTS OF VARIOUS TISSUES FROM HUMANS, RABBITS,  
AND GUINEA PIGS

SOURCE	BRAIN		HEART		LUNG		LIVER		KIDNEY		MUSCLE		SPLEEN	
	ANTI- COMP. 1:5	ANTI- GENIO 1:20	ANTI- COMP. 1:5	ANTI- GENIO 1:20	ANTI- COMP. 1:5	ANTI- GENIO 1:20	ANTI- COMP. 1:5	ANTI- GENIO 1:20	ANTI- COMP. 1:5	ANTI- GENIO 1:20	ANTI- COMP. 1:5	ANTI- GENIO 1:20	ANTI- COMP. 1:5	ANTI- GENIO 1:20
Human	0.7	—*	0.7	0.4	0.5	—	0.5	0.6	0.7	—	0.3	—	0.6	—
Rabbit	—**	—	—	—	—	—	—	—	—	—	—	—	—	—
Guinea Pig	0.8	—	0.6	0.4	0.4	—	0.7	0.5	0.3	0.6	0.8	—	0	0

\*=Not perfectly antigenic in 1 c.c. of 1:20 dilution.  
\*\*=Complete hemolysis (not anticomplementary) in 1 c.c. of 1:5 dilution.

these, and both, particularly the former, are not as satisfactory for the conduct of the Wassermann test as alcoholic extracts of tissues.

In our experiments we have prepared and tested alcoholic ex-

TABLE VIII

THE HEMOLYTIC ACTIVITY OF ALCOHOLIC EXTRACTS OF HUMAN, BEEF AND GUINEA PIG HEART MUSCLE

HEART	1 DAY		2 DAYS		3 DAYS		4 DAYS		8 DAYS	
	95	ABSO.	95	ABSO.	95	ABSO.	95	ABSO.	95	ABSO.
	ALC.	ALC.	ALC.	ALC.	ALC.	ALC.	ALC.	ALC.	ALC.	ALC.
Beef No. 1	—*	—	—	—	—	—	—	—	—	—
Beef No. 2	—	—	—	—	—	—	—	—	—	—
Beef No. 3	—	—	—	—	—	—	—	—	—	—
Beef No. 4	—	—	—	—	—	—	—	—	—	—
Beef No. 5	—	—	—	—	—	—	—	—	—	—
Beef No. 6	—	—	—	—	—	—	—	—	—	—
Human No. 1	—	—	—	—	—	—	—	—	0.5	0.4
Human No. 2	—	—	—	—	—	—	—	—	—	0.5
Human No. 3†	0.3**	0.2	0.3	0.2	0.3	0.2	0.3	0.2	0.2	0.1
Human No. 4	0.3	0.2	0.2	0.2	0.1	0.2	0.2	0.2	0.2	0.1
Human No. 5	—	—	—	—	—	—	—	—	—	—
Human No. 6	0.3	0.2	0.2	0.2	0.1	0.2	0.2	0.2	0.1	0.2
G. pig No. 1	—	—	—	—	—	—	—	—	—	—
G. pig No. 2	—	—	—	—	—	—	—	—	—	—

\*=not hemolytic in amount of 0.5 c.c. 1:10 dilution of extract.

\*\*=amount of extract diluted 1:10 producing slight hemolysis (*minimal* hemolytic unit).  
†=hearts No. 3, 4 and 6 had undergone advanced postmortem changes, being left at room temperature for forty-eight hours after removal.

TABLE IX

THE ANTICOMPLEMENTARY ACTIVITY OF ALCOHOLIC EXTRACTS OF HUMAN, BEEF GUINEA PIG HEART MUSCLE

HEART	1 DAY		2 DAYS		3 DAYS		4 DAYS		8 DAYS	
	95	ABS.	95	ABS.	95	ABS.	ABS.	ABS.	95	ABS.
	ALC.	ALC.	ALC.	ALC.	ALC.	ALC.	ALC.	ALC.	ALC.	ALC.
Beef No. 1	—*	—	—	—	—	—	—	—	—	—
Beef No. 2	—	—	—	—	—	—	—	—	—	0.5
Beef No. 3	—	—	—	—	—	—	—	—	0.5	0.5
Beef No. 4	—	—	—	—	—	—	—	—	0.5	0.5
Beef No. 5	—	—	—	—	—	—	—	—	0.5	0.5
Beef No. 6	—	—	—	—	—	—	—	—	—	0.4
Human No. 1	—	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Human No. 2	—	—	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Human No. 3	0.5**	0.4	0.4	0.3	0.5	0.3	0.5	0.3	0.4	0.3
Human No. 4	—	—	0.5	0.4	0.5	0.3	0.5	0.3	0.5	0.2
Human No. 5	—	—	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Human No. 6	0.4	0.4	0.3	0.5	0.5	0.5	0.5	0.4	0.3	0.3
G. pig No. 1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
G. pig No. 2	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1

\*=not anticomplementary in 0.5 c.c. 1:10 dilution.

\*\*=smallest amount of extract 1:10 producing *beginning inhibition of hemolysis*.

TABLE X

THE ANTIGENIC ACTIVITY OF ALCOHOLIC EXTRACTS OF HUMAN, BEEF AND GUINEA PIG HEART MUSCLE

HEART	1 DAY		2 DAYS		3 DAYS		4 DAYS		8 DAYS	
	95 ALC.	ABS. ALC.	95 ALC.	ABS. ALC.	95 ALC.	ABS. ALC.	95 ALC.	ABS. ALC.	95 ALC.	ABS. ALC.
Beef No. 1	-*	-	-	-	-	-	-	-	1:100**	1:100
Beef No. 2	-	-	-	-	-	-	-	-	1:100	1:100
Beef No. 3	-	-	-	-	-	-	-	-	1:100	1:100
Beef No. 4	-	-	-	-	-	-	-	-	1:100	1:200
Beef No. 5	-	-	-	-	-	-	-	-	1:100	1:200
Beef No. 6	-	-	-	-	-	-	-	-	1:100	1:100
Human No. 1	-	-	-	-	-	-	-	-	1:100	1:200
Human No. 2	-	-	-	-	-	-	-	-	1:100	1:100
Human No. 3	-	-	-	-	-	-	-	-	1:100	1:200
Human No. 4	-	-	-	-	-	-	-	-	1:200	1:200
Human No. 5	-	-	-	-	-	-	-	-	1:200	1:100
Human No. 6	-	-	-	-	-	-	-	-	1:200	1:200
G. pig No. 1	-	-	-	-	-	-	-	-	1:100	1:100
G. pig No. 2	-	-	-	-	-	-	-	-	1:100	1:100

\*Not perfectly antigenic in 0.2 c.c. of 1:50.

\*\*Perfectly antigenic in amounts of 0.2 c.c.

tracts of the brain, heart, lung, liver, kidney and thigh muscles of persons, rabbits and guinea pigs; all tissues were used fresh, minced to the same degree, used in the same proportions, extracted at the same time and in the same incubator and titrated at the same time for hemolytic, anticomplementary and antigenic activities at varying intervals (Table VII).

The results of these experiments have shown the following:

1. Rabbit tissues are decidedly inferior to those of human beings and guinea pigs for the preparation of extracts.

2. Heart, liver and kidney tissue proved best for the preparation of extracts, named in the order of preference. Extracts of the brain, lung and muscle proved very poor from the standpoint of antigenic activity.

3. Extracts of fresh beef heart were generally more satisfactory than corresponding extracts of human heart; extracts of human muscle which had undergone postmortem changes were unsatisfactory owing to high degree of hemolytic activity (Nos. 3, 4 and 6 in Table VIII). Extracts of human heart muscle generally acquired more anticomplementary substances and more quickly than corresponding extracts of beef hearts. These differences may have

been due to the fact that the beef hearts were perfectly fresh and used within a few hours after removal.

4. *Extracts of guinea pig heart were usually highly anticomplementary and inferior to extracts of beef and human heart.*

Extracts of different beef and human hearts prepared at the same time and in exactly the same manner, varied to a slight degree in antigenic activity (Table X).

Of the tissues included in this study *extracts of beef and human heart have proved most satisfactory*; Noguchi, Browning and McKenzie and others have found beef liver satisfactory for the extraction of lecithins, but for plain alcoholic extracts heart muscle is to be preferred. Ruediger<sup>59</sup> found extracts of dog and guinea pig heart highly anticomplementary or, at least, especially likely to yield nonspecific reactions. In our experience *fresh beef heart muscle (fat free) has been found generally most satisfactory for the preparation of plain alcoholic extracts and especially mixtures of the muscle of several hearts, which is readily obtainable if dried muscle powder is employed.*

*The Alcoholic Extraction of Dried Versus Wet Tissues.*—Dried tissues and particularly fetal syphilitic liver and beef heart muscle, have been used by a few workers for many years for the purpose of extraction with acetone or alcohol.

The principal advantages are the *finely divided state* of the material, facilitating the extraction of intracellular substances and particularly phosphatids (Erlandsen) and *convenience*; large amounts of muscle may be ground and dried at one time and readily kept in glass-stoppered bottles. The method also facilitates the *use of mixtures* of muscle from different hearts, which has a slight advantage over the use of the muscle of one heart for the preparation of an extract.

The main disadvantage is that alcoholic extracts of dried muscle are quantitatively *more hemolytic* than extracts of wet tissue; the extraction of dried muscle with ether removes a large part but not all, of these hemolytic substances. Rapid drying in a vacuum apparatus yields a product less hemolytic than material slowly dried at room temperature; for this reason we believe that autolytic changes facilitated by slow drying result in the production of these hemolytic substances.

*The Amount of Tissue Extracted.*—The proper amount of wet or dried human or beef heart tissue to employ for alcoholic extraction

would appear to be from four to ten gm. per 100 c.c. of alcohol (Table XV); less tissue yields an extract of comparatively weak antigenic activity. The use of more than ten gm. of tissue results in increasing the hemolytic and anticomplementary activities of some extracts without an appreciable gain in antigenic activity; we have used ten grams ether extracted powder for each 100 c.c. of 95 or absolute alcohol with success and general satisfaction.

*The Influence of Reenforcing Tissue Extracts with Cholesterin.*—While alcoholic solutions of cholesterin are at best feebly antigenic, undoubtedly the addition of cholesterin to alcoholic extracts of tissues greatly improves antigenic activity. As far as we know all serologists agree with this statement, but a few are of the opinion that such cholesterin reinforced extracts may yield nonspecific reactions.

The amount of cholesterin used by different workers varies rather widely; for example, Browning and McKenzie add 1 or 1.2 grams to each 100 c.c. of their 0.75 per cent solutions of liver lecithins in ethyl alcohol; Sachs uses 0.1 per cent or less added to alcoholic extracts of heart; Walker and Swift regard 0.4 per cent as optimum for alcoholic extracts of heart and the majority of serologists in this country have apparently adopted this practice. Field uses alcoholic extracts of heart muscle one-half saturated with cholesterin; Neymann and Gager use 0.2 per cent solutions in alcoholic extracts of heart. Cholesterin being antihemolytic usually increases the anticomplementary activity of tissue extracts; the object of our experiments was to determine the minimal amount necessary to *stabilize* extracts and enhance their antigenic activity without greatly increasing anticomplementary activity.

With this end in view a large number of experiments were conducted, the results of a few being shown in Tables XI to XV, which may be summarized as follows:

1. Solutions of cholesterin in plain ethyl alcohol are more anticomplementary than in alcoholic extracts of heart due presumably to the presence of hemolytic substances in the latter (Table XI).

2. The addition of 0.1 to 0.2 grams pure cholesterin to 100 c.c. alcoholic extracts of heart is apparently sufficient to stabilize the antigen and render it highly antigenic; this is shown in Tables XII, XIII and XIV. Occasionally the addition of more cholesterin up to 0.4 per cent results in enhancing antigenic activity to a

slightly greater degree, but this also increases anticomplementary activity and accordingly the chances for nonspecific reactions.

The results shown in Table XII were observed with alcoholic extracts of human and beef heart alone and reenforced with 0.4, 0.3, 0.2, 0.1 and 0.05 per cent pure cholesterin and titrated with a

TABLE XI

THE ANTICOMPLEMENTARY AND ANTIGENIC ACTIVITY OF CHOLESTERIN ALONE IN ALCOHOL AND IN ALCOHOLIC EXTRACTS OF HEART MUSCLE

PER CENT CHOLESTERIN	ABSOLUTE ALCOHOL		ALCOHOLIC EXTRACT OF BEEF HEART	
	ANTICOMPLEMENTARY UNIT	ANTIGENIC UNIT	ANTICOMPLEMENTARY UNIT	ANTIGENIC UNIT
0.1	0.6 of 1:20	—**	—*	0.5 of 1:20
0.2	0.4 of 1:20	—**	—*	0.3 of 1:20
0.3	0.2 of 1:20	—**	—*	0.3 of 1:20
0.4	0.2 of 1:20	—**	—*	0.2 of 1:20

\*Not anticomplementary in 2 c.c. of 1:20.

\*\*Not antigenic in 0.5 c.c. of 1:20.

TABLE XII

THE INFLUENCE OF CHOLESTERIN UPON THE ANTICOMPLEMENTARY AND ANTIGENIC ACTIVITIES OF ALCOHOLIC EXTRACTS OF HEART MUSCLE

CHOLESTERIN ADDED TO EXTRACTS	ALCOHOLIC EXTRACT HUMAN HEART		ALCOHOLIC EXTRACT BEEF HEART	
	ANTICOMPLEMENTARY UNIT	ANTIGENIC UNIT	ANTICOMPLEMENTARY UNIT	ANTIGENIC UNIT
None	—*	0.1 of 1:50	—*	0.1 of 1:50
0.05 per cent	—*	0.1 of 1:200	—*	0.1 of 1:50
0.1 per cent	0.5 of 1:10	0.1 of 1:200	0.5 of 1:10	0.1 of 1:200
0.2 per cent	0.5 of 1:10	0.1 of 1:200	0.5 of 1:10	0.1 of 1:200
0.3 per cent	0.4 of 1:10	0.1 of 1:200	0.4 of 1:10	0.1 of 1:200
0.4 per cent	0.3 of 1:10	0.1 of 1:300	0.3 of 1:10	0.1 of 1:200

\*Not anticomplementary in 0.5 c.c. of 1:10.

TABLE XIII

THE RELATION OF AMOUNT OF CHOLESTERIN ADDED TO ALCOHOLIC EXTRACTS TO ANTIGENIC ACTIVITY\*

EXTRACTS	AMOUNTS SERUM			
	0.1	0.025	0.006	0.0015
Alc. Ext. Beef Heart (Plain)	++++	++++	++	—
“ “ “ “ +0.4 cholest.	++++	++++	++++	+
“ “ “ “ +0.3 cholest.	++++	++++	++++	+
“ “ “ “ +0.2 cholest.	++++	++++	++++	+
“ “ “ “ +0.1 cholest.	++++	++++	++++	+
“ “ “ “ +0.05 cholest.	++++	++++	+++	—

\*Primary incubation 18 hours at 3° C.

TABLE XIV

THE RELATION OF AMOUNT OF CHOLESTERIN ADDED TO ALCOHOLIC EXTRACTS TO ANTIGENIC ACTIVITY\*

EXTRACTS	UNITS OF COMPLEMENT FIXED					
	2	4	6	8	10	12
Ale. Ext. Beef Heart (Plain)	++++	++++	+	-	-	-
" " " " + 0.4 cholest.	++++	++++	++++	+	-	-
" " " " + 0.4 cholest.	++++	++++	++++	+	-	-
" " " " + 0.3 cholest.	++++	++++	++++	+	-	-
" " " " + 0.2 cholest.	++++	++++	++++	+	-	-
" " " " + 0.1 cholest.	++++	++++	++++	+	-	-
" " " " + 0.05 cholest.	++++	++++	++++	-	-	-

\*Primary incubation 18 hours at 8° C.

mixture of syphilitic sera for antigenic activity. In Tables XIII and XIV the extracts were used in dose of four antigenic units with varying amounts of syphilitic serum. The results of these and numerous other experiments of a similar character showed that *the addition of 0.1 or 0.2 gram pure cholesterol to 100 c.c. alcoholic extracts of beef or human heart imparted the maximum or almost the maximum of antigenic activity and, in our opinion, constitutes sufficient for gaining all the advantages to be derived from cholesterolizing tissue extracts.*

## Part 2

### *The Comparative Antigenic, Anticomplementary and Hemolytic Activities of Organ Extracts*

*Comparative Antigenic Activities.*—The following four methods are available for determining the comparative antigenic activity of tissue extracts:

1. By using each extract in varying amounts with constant amounts of syphilitic serum and complement to determine the antigenic unit or smallest amount of antigen giving complete inhibition of hemolysis.

2. By using each extract in constant amount of two or five antigenic units as determined in 1 with a constant amount of complement and varying amounts of syphilitic serum.

3. By using each extract in constant amount of two or five antigenic units with a constant amount of syphilitic serum and a varying number of units of complement.

4. By routine Wassermann tests with a large number of sera.

CHART I.—COMPARATIVE ANTIGENIC ACTIVITY OF TISSUE EXTRACTS

Extract 0.1 c.c.	Alcoholic Syphilitic Liver	Alcoholic Beef Heart	Acetone Insoluble Lipoids	Cholesterolized Alcoholic Beef Heart	Lecithins plus Cholesterin
1:500					
1:400					
1:300					
1:200					
1:100					
1:50					
1:25					
Primary incub. #	W R	W R	W R	W R	W R

#W = water-bath 1 hour; R = refrigerator 8° C. for 18 hours.

CHART 2.—THE COMPARATIVE ANTIGENIC ACTIVITY OF EXTRACTS AT 38° C. FOR ONE HOUR.

Degree Fixation	Plain Human Heart	Plain Beef Heart	Plain Syph. Liver	Acetone Insoluble Lipoids	Cholest. Human Heart#	Cholest. Beef Heart#	Cholest. Beef Heart#	Acet.Insol. Lipoids + Cholest.##
4.0								
3.8								
3.6								
3.4								
3.2								
3.0								
2.8								
2.6								
2.4								
2.2								
2.0								
1.8								
1.6								
1.4								

#0.4 per cent cholesterin.

##0.2 per cent cholesterin.



We have employed the first three methods in comparative studies of a large number of different extracts; while the fourth method is the one generally employed, it is subject to error in mistaken clinical diagnoses, whereas with the first three methods only sera from absolutely known cases of syphilis are employed.

Furthermore the method of primary incubation influences the results, that is, cold incubation increases the antigenic activity of all extracts, but especially of the plain or crude alcoholic extracts; in our experiments both warm (water-bath, one hour) and cold (refrigerator, eighteen hours) incubation were employed.

All experiments were conducted with *mixtures* of fresh sera from six or more luetic individuals; likewise mixed guinea pig serum complements were employed with an antish sheep hemolytic system, the details of technic being described in a separate article.<sup>56</sup> All extracts were prepared of wet tissues.

As previously stated the extracts in common use are plain or crude alcoholic extracts of heart (human, beef or guinea pig), cholesterolized alcoholic extracts of heart and acetone insoluble lipoids of heart or liver; to these may be added a fourth, namely, an extract of alcoholic solutions of lecithins plus cholesterolin (Browning and McKenzie; Neymann and Gager).

The results of an experiment with four of these extracts tested for antigenic activity according to the first method in a water-bath at 38° C. for one hour and in a refrigerator at 8° C. for eighteen hours, are shown in Chart 1.

Charts 2, 3, 4 and 5 give the results of experiments conducted after the second method and Chart 6, the results obtained with the third method.

The general results may be summarized as follows:

1. Cholesterolized extracts are most antigenic at both 38° C. and 8° C.; next in order of sensitiveness are acetone insoluble lipoids and plain alcoholic extracts at both temperatures.
2. Extracts containing 0.2 per cent cholesterolin are usually, but not always, as antigenic as those containing 0.4 per cent.
3. Mixtures of lecithins (acetone insoluble lipoids) and cholesterolin are highly antigenic and usually as much so as alcoholic extracts of heart reenforced with 0.2 to 0.4 per cent cholesterolin.

*Comparative Anticomplementary Activities.*—In all experiments an antish sheep hemolytic system with two units of complement and

CHART 3.—COMPARATIVE ANTIGENIC ACTIVITY OF DIFFERENT ORGAN EXTRACTS AT 38° C. FOR ONE HOUR.

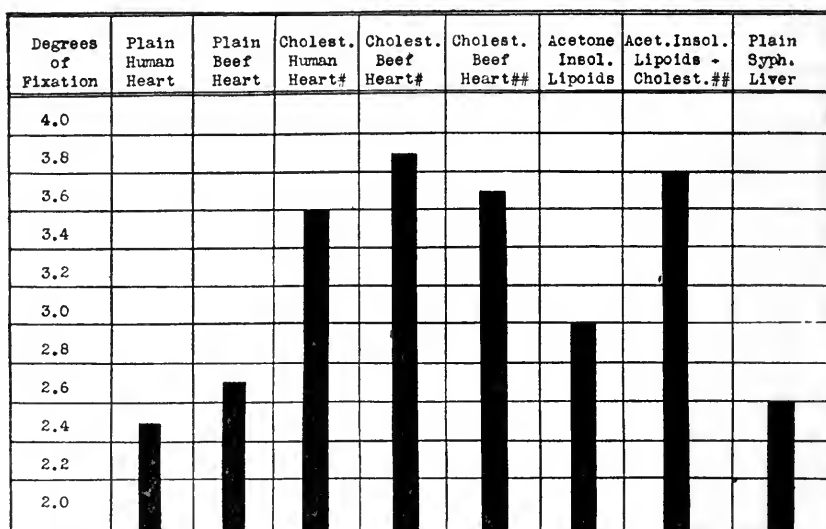


CHART 4.—COMPARATIVE ANTIGENIC ACTIVITY OF DIFFERENT ORGAN EXTRACTS IN A WATER-BATH AT 38° C. FOR ONE HOUR.

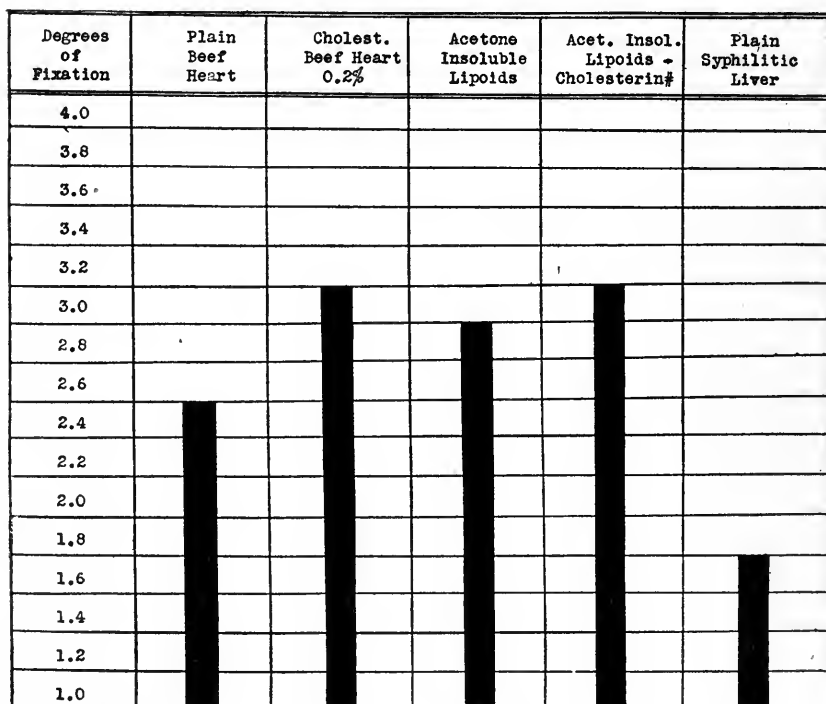
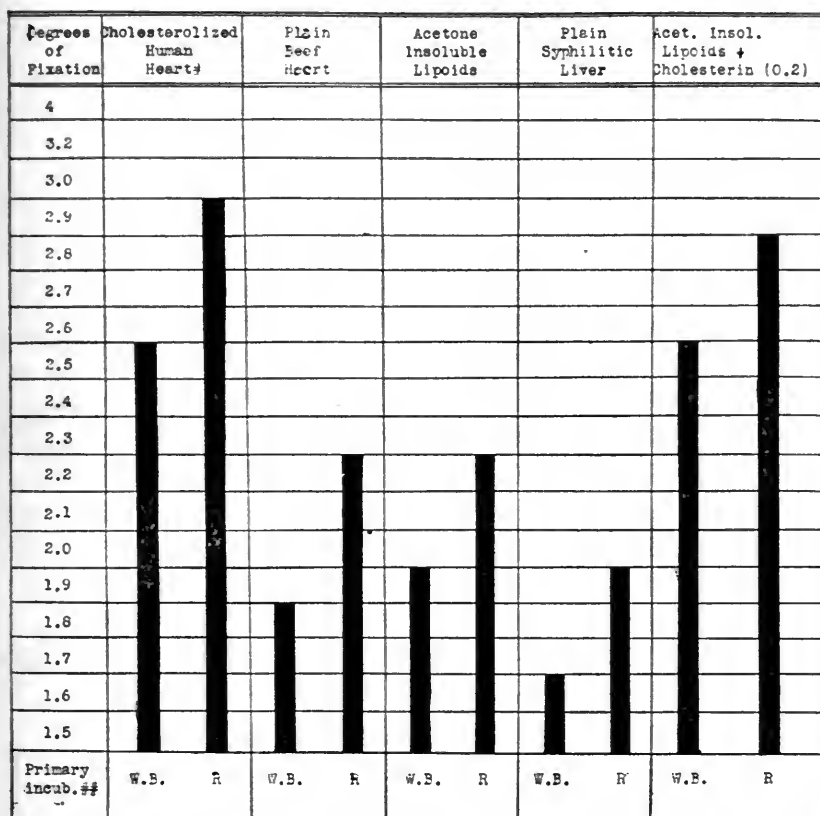


CHART 5.—COMPARATIVE ANTIGENIC SENSITIVENESS OF FIVE DIFFERENT EXTRACTS



±0.4 per cent.

## W. B. = water-bath at 38° C. for 1 hour. R = refrigerator at 8° for 18 hours.

CHART 6.—COMPARABLE ANTIGENIC ACTIVITY OF ORGAN EXTRACTS AT 8° C FOR 18 HOURS.

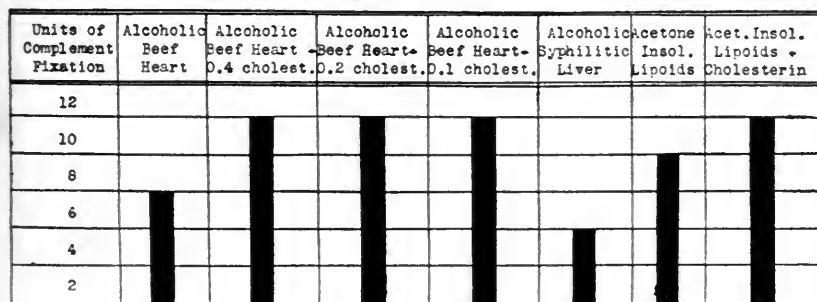


CHART 7.—THE ANTICOMPLEMENTARY ACTIVITY OF TISSUE EXTRACTS AT 38° C. FOR ONE HOUR AND AT 8° C. FOR 18 HOURS.

Extract 1:10	Alcoholic Extract Beef Heart	Cholest. Extract Beef Heart#	Cholest. Extract Beef Heart##	Acetone Insoluble Lipoids	Alcoholic Extract Syph. Liver	Lecithin Cholesterin
0.1						
0.2						
0.3						
0.4						
0.5						
0.6						
0.7						
0.8						
0.9						
1.0						
Primary incub.###	W R	W R	W R	W R	W R	W R

#0.4 per cent cholesterin.

##0.2 per cent cholesterin.

###W = water-bath 1 hour; R = refrigerator 18 hours.

CHART 8.—THE HEMOLYTIC ACTIVITY OF TISSUE EXTRACTS AT 38° C. FOR ONE HOUR.

Extract 1:5	Alcoholic Extract Beef Heart	Cholest. Extract Beef Heart#	Cholest. Extract Beef Heart##	Acetone Insoluble Lipoids	Alcoholic Extract Syph. Liver	Lecithin + Cholesterin
0.1						
0.2						
0.3						
0.4						
0.5						
0.6						
0.7						
0.8						
0.9						
1.0						

#0.4 per cent cholesterin.

##0.2 per cent cholesterin.

one unit of hemolysin were employed, the details being given in a separate article. All extracts were prepared of wet tissues and slowly diluted with saline solution in a uniform manner.

The results of a part of one experiment are shown in Chart 7, as an example of a series. These have been summarized as follows:

Extracts of acetone insoluble lipoids of fresh beef heart prepared after the method of Noguchi in 3 per cent solutions in methyl alcohol, were least anticomplementary at both 38° C. and 8° C.; next in order were mixtures of acetone insoluble lipoids and cholesterolin, plain alcoholic extracts of heart, alcoholic extracts of syphilitic liver, 0.2 and 0.4 per cent cholesterolin reenforced heart extracts.

*Comparative Hemolytic Activities.*—Various substances in alcoholic

TABLE XV

THE RELATION OF AMOUNT OF DRIED TISSUE EXTRACTED TO PROPERTIES OF ORGAN EXTRACT

DRIED TISSUE PER 100 C.C. 95 ALC.	DRIED HUMAN HEART EXTRACT		DRIED BEEF HEART EXTRACT	
	ANTICOMPLEMENTARY UNIT	ANTIGENIC UNIT (1:50)	ANTICOMPLEMENTARY UNIT	ANTIGENIC UNIT (1:50)
0.5 gm.	—*	0.25	—	0.5
1.0 gm.	—	0.15	—	0.5
2.0 gm.	—	0.12	—	0.4
4.0 gm.	—	0.1	—	0.3
6.0 gm.	—	0.1	—	0.25
10.0 gm.	—	0.08	—	0.2

\*Not anticomplementary in amount of 1.5 c.c. of 1:10.

Table XVI

THE INFLUENCE OF CHOLESTERIN UPON THE ANTICOMPLEMENTARY AND ANTIGENIC ACTIVITIES OF ALCOHOLIC EXTRACTS OF BEEF HEART

METHOD OF PREPARING EXTRACTS	PER CENT CHOLEST.	EXTRACT No. 1		EXTRACT No. 2	
		ANTI-COMPL. UNIT 1:10	ANTI-GENIC UNIT 1:10	ANTI-COMPL. UNIT 1:10	ANTI-GENIC UNIT 1:10
Plain extract alone	0	1.2 c.c.	0.3 c.c.	0.6 c.c.	—**
Extract 2 parts; cholest. Sol. 1 part*	0.1	1.2 c.c.	0.15 c.c.	0.6 c.c.	0.1 c.c.
Extract 1 part; cholest. Sol. 1 part*	0.2	1.2 c.c.	0.1 c.c.	0.5 c.c.	0.07 c.c.
Extract 1 part; cholest. Sol. 2 parts*	0.3	1.0 c.c.	0.1 c.c.	0.4 c.c.	0.07 c.c.
Extract +0.4 per cent cholest.	0.4	1.0 c.c.	0.07 c.c.	0.3 c.c.	0.04 c.c.

\*Cholesterolin solution; 0.4 per cent in absolute ethyl alcohol.

\*\*Not antigenic in 0.5 c.c. of 1:10.

extracts of tissues are regarded as possessing hemolytic properties; chief among these are the soaps and fatty acids.

Hemolytic activity of extracts of different tissues of the same kind and prepared in exactly the same manner are known to vary, but the object of our experiments was to test a sufficient number representing the four main kinds to permit of broad comparison and conclusions. The results of an experiment shown in Chart 8, are representative of all tests of this kind and show the comparative hemolytic activities of different extracts for 0.2 c.c. of 5 per cent suspensions of sheep cells in a total volume of 2 c.c. and an exposure of one hour at 38° C. in a water-bath.

These experiments have shown that extracts of acetone insoluble lipoids (lecithins) and mixtures of these with cholesterin are least hemolytic; next in order are cholesterolized alcoholic extracts of heart, plain alcoholic extracts of heart and alcoholic extracts of fetal liver, the latter being usually most hemolytic due, probably, to the presence of autolytic products in addition to a high content of fatty acids and soaps.

#### SUMMARY AND CONCLUSIONS

1. Alcoholic extracts of various tissues were more antigenic but at the same time more hemolytic and anticomplementary, than saline extracts of the same tissues prepared in the same manner.
2. Ethereal extracts of tissues are usually so highly hemolytic as to exclude their use as antigens, although they are frequently highly antigenic, due to the presence of phosphatids.
3. Acetone extracts of tissues are usually less antigenic than alcoholic extracts.
4. Absolute ethyl alcohol is slightly superior to 95 per cent alcohol for the preparation of extracts.
5. Highest purity methyl alcohol is as good as absolute ethyl alcohol for the extraction of dried tissues; ethyl alcohol is better for the extraction of fresh or wet tissues.
6. Tissues may be satisfactorily extracted with alcohol at temperatures varying from 6° C. to 38° C.; the latter temperature yields extracts of somewhat superior antigenic activity in a shorter period of time.
7. At 38° C. wet and dried tissues should be extracted with alcohol for at least five to eight days to secure the maximum of

antigenic activity; extracts prepared with boiling alcohol for one to three hours, usually possess but slight antigenic activity.

8. Alcoholic extracts of brain, heart, lung, kidney, liver and muscle of persons, cattle, rabbits and guinea pigs, prepared in an identical manner and at the same time have shown: (a) rabbit tissues are decidedly inferior to those of persons, cattle and guinea pigs for the preparation of antigens; (b) heart, liver and kidney tissue yield better antigens than brain, lung and muscle; (c) beef heart generally yields better antigen than human heart, because extracts of human heart are frequently highly hemolytic and (d) extracts of guinea pig heart are frequently highly anticomplementary. Of all tissues included in this study best antigens were secured from beef and human heart muscle. If the latter are fresh and not too fatty the extracts are of about equal excellence; otherwise fresh beef heart muscle is to be preferred.

9. Alcoholic extracts of different human hearts and different beef hearts prepared at the same time and in an identical manner, varied slightly in antigenic activity.

10. Alcoholic extracts of dried tissues (heart muscle) are usually more hemolytic than extracts of fresh wet tissues; extracts of tissues dried rapidly are somewhat less hemolytic than extracts of tissues dried slowly.

11. For the extraction of wet or dried tissues with alcohol, best antigens are generally secured by using from four to ten gm. of tissue for each 100 c.c. alcohol.

12. The addition of pure cholesterin to alcoholic extracts of normal tissues undoubtedly serves to stabilize the extracts and greatly increases the antigenic activity; for these purposes 0.1 to 0.2 gm. cholesterin for each 100 c.c. alcoholic extract is sufficient. More cholesterin increases the anticomplementary activity and renders extracts liable to yield nonspecific reactions.

13. Comparative studies of the antigenic, anticomplementary and hemolytic properties of four different kinds of extracts namely, plain or crude extracts of syphilitic liver and nonsyphilitic tissues, cholesterolized alcoholic extracts of normal tissues, acetone insoluble lipoids of normal tissues, and mixtures of acetone insoluble lipoids and cholesterin, tested at both 38° C. for one hour and 8° C. for eighteen hours, have shown that the best antigens are mixtures of acetone insoluble lipoids (lecithins) and cholesterin; next in order

are alcoholic extracts of beef or human heart reenforced with 0.2 to 0.4 per cent cholesterin, acetone insoluble lipoids, plain alcoholic extracts of beef or human heart and lastly, alcoholic extracts of fetal syphilitic liver.

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## STUDIES IN THE STANDARDIZATION OF THE WASSERMANN REACTION, XXVI\*

### A STUDY OF METHODS FOR THE PRESERVATION OF TISSUE EXTRACTS (ANTIGENS)

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(Received for publication, November 30, 1920.)

AS is well known tissue extracts employed as antigens in complement-fixation tests for syphilis, may suddenly and unaccountably acquire enhanced anticomplementary activities or, less frequently, lose in antigenic sensitiveness. The reasons for these changes are not understood insofar at least as concerns alcoholic extracts; with saline extracts, bacterial contamination and changes in protein content are probably responsible in some degree for an increase of anticomplementary activity.

To avoid these changes tissue extracts are usually kept in a refrigerator; this practice was originally advocated by Wassermann for the preservation of saline extracts of fetal syphilitic liver and has since become the general custom for the preservation of alcoholic extracts as well. A few serologists however, preserve antigens in an incubator or at room temperature and particularly alcoholic extracts reenforced with cholesterin, to avoid the precipitation of cholesterin and other lipoidal substances at low temperatures.

Probably the majority of serologists prefer freshly prepared emulsions made by diluting alcoholic extracts of tissues with physiologic saline solution for each day's work; others however, apparently use these emulsions over a period of several days and even weeks for the purposes of economy and convenience.

#### PURPOSES OF INVESTIGATION

The purposes of our investigation were to determine:

1. If the temperature at which alcoholic extracts of tissues were

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\*Investigation aided by funds accruing from the preparation of arsphenamine.

kept had any influence upon the preservation of their antigenic, anticomplementary or hemolytic activities.

2. If there were any differences in the antigenic, anticomplementary or hemolytic activities of saline dilutions of various tissue extracts preserved over a period of several weeks as compared with freshly prepared emulsions.

We have not studied the causes of changes in the anticomplementary activity of alcoholic extracts of tissues or of changes in antigenic activity, which constitutes a problem of considerable practical importance, but have confined our studies to the two propositions mentioned above as bearing upon the preservation of alcoholic tissue extracts and saline dilutions of these, for a standardized complement-fixation test in syphilis.

## Part 1

### THE INFLUENCE OF TEMPERATURE UPON THE PRESERVATION OF ALCOHOLIC EXTRACTS OF TISSUES

The following extracts were divided into three parts and kept in a refrigerator at 6°-8° C., in a laboratory at 20°-22° C. and in an incubator at 37° C. with due precautions against evaporation:

Plain alcoholic extract of human heart

Plain alcoholic extract of beef heart

Cholesterolized alcoholic extract of human heart

Cholesterolized alcoholic extract of beef heart

Acetone insoluble lipoids of beef heart in 3 per cent solution in methyl alcohol.

Acetone insoluble lipoids and cholesterolin<sup>1</sup>

Titration were made of the three portions of each of these six extracts after five, nine, fourteen, twenty-two and twenty-eight days; an antisheep hemolytic system was employed, the technic being described in a separate article.<sup>2</sup> It may be stated here that each extract was diluted with saline solution in a uniform manner and every precaution observed to render the tests strictly comparative.

1. *Influence upon Antigenic Activity.*—In making these titrations different syphilitic sera were used on the fifth, ninth, fourteenth days, etc.; therefore the antigenic activities of the extracts on the fifth day cannot be compared with those on the ninth day and so forth, but *the antigenic activities of the three portions of each of*

*the six extracts kept at varying temperatures, are strictly comparative.*

The results of a set of titrations given in Tables I, II, III, IV and V show the *highest dilutions* of each of the three portions of the six

TABLE I

THE INFLUENCE OF TEMPERATURE UPON THE PRESERVATION OF ANTIGENIC ACTIVITY OF TISSUE EXTRACTS

EXTRACTS	KEPT FOR 5 DAYS AT		
	8° C.	22° C.	38° C.
Plain alc. human heart	1:200*	1:100	—
Plain alc. beef heart	1:100	1:100	1:100
Cholest. human heart	1:300	1:200	1:200
Cholest. beef heart	1:200	1:300	1:100
Acetone Insoluble Lipoids	1:800	1:400	1:100
Acetone Insoluble Lipoids + Cholest.	1:300	1:100	1:100

\*Highest dilution in amount of 0.2 c.c. proving perfectly antigenic; — not completely antigenic in 0.2 c.c. of 1:50.

TABLE II

THE INFLUENCE OF TEMPERATURE UPON THE PRESERVATION OF ANTIGENIC ACTIVITY OF TISSUE EXTRACTS

EXTRACTS	KEPT FOR 9 DAYS AT		
	8° C.	22° C.	38° C.
Plain alc. human heart	1:200*	1:50	1:50
Plain alc. beef heart	1:50	1:50	1:50
Cholest. human heart	1:200	1:200	1:100
Cholest. beef heart	1:200	1:200	1:100
Acetone Insoluble Lipoids	1:400	1:400	1:400
Acetone Insoluble Lipoids + Cholest.	1:200	1:200	1:200

\*Highest dilution in amount of 0.2 c.c. proving perfectly antigenic.

TABLE III

THE INFLUENCE OF TEMPERATURE UPON THE PRESERVATION OF ANTIGENIC ACTIVITY OF TISSUE EXTRACTS

EXTRACTS	KEPT FOR 14 DAYS AT		
	8° C.	22° C.	38° C.
Plain alc. human heart	1:50*	1:50	—
Plain alc. beef heart	1:50	1:50	1:50
Cholest. human heart	1:50	1:50	1:50
Cholest. beef heart	1:50	1:50	1:50
Acetone Insoluble Lipoids	1:200	1:100	1:100
Acetone Insoluble Lipoids + Cholest.	1:100	1:50	1:50

\*Highest dilution in amount of 0.2 c.c. proving perfectly antigenic; — not completely antigenic in 0.2 c.c. of 1:50.

TABLE IV

THE INFLUENCE OF TEMPERATURE UPON THE PRESERVATION OF ANTIGENIC ACTIVITY OF TISSUE EXTRACTS

EXTRACTS	KEPT FOR 22 DAYS AT		
	8° C.	22° C.	38° C.
Plain alc. human heart	1:50*	1:50	—
Plain alc. beef heart	1:50	1:50	—
Cholest. human heart	1:50	1:50	1:50
Cholest. beef heart	1:200	1:100	1:100
Acetone Insoluble Lipoids	1:50	1:50	1:50
Acetone Insoluble Lipoids + Cholest.	1:100	1:100	1:100

\*Highest dilution in amount of 0.2 c.c. proving perfectly antigenic.

TABLE V

THE INFLUENCE OF TEMPERATURE UPON THE PRESERVATION OF ANTIGENIC ACTIVITY OF TISSUE EXTRACTS

EXTRACTS	KEPT FOR 28 DAYS AT		
	8° C.	22° C.	38° C.
Plain alc. human heart	1:50*	—	—
Plain alc. beef heart	1:50	—	—
Cholest. human heart	1:100	1:100	1:100
Cholest. beef heart	1:200	1:100	1:100
Acetone Insoluble Lipoids	1:300	1:300	1:100
Acetone Insoluble Lipoids + Cholest.	1:300	1:200	1:200

\*Highest dilution in amount of 0.2 c.c. proving perfectly antigenic.

extracts proving perfectly antigenic in amounts of 0.2 c.c. with 0.05 c.c. of heated syphilitic serum.

In a duplicate set of experiments the extracts were titrated by using varying amounts of 1:100 dilutions with 0.05 c.c. syphilitic serum; the results with three of the extracts are given in Tables VI, VII and VIII as examples. These tables give the smallest amount of 1:100 dilutions of each portion of the various extracts proving perfectly antigenic.

The results of these experiments have shown that *extracts kept*

TABLE VI

THE INFLUENCE OF TEMPERATURE UPON THE PRESERVATION OF A PLAIN ALCOHOLIC EXTRACT OF BEEF HEART

PRESERVATION DAYS	REFRIGERATOR 8° C.		ROOM (20° C.)		INCUBATOR (37° C.)	
	ANTICOMPL.	ANTIGENIC	ANTICOMPL.	ANTIGENIC	ANTICOMPL.	ANTIGENIC
	1:10	1:100	1:10	1:100	1:10	1:100
1	1.0	0.2	1.0	0.2	1.0	0.2
7	0.7	0.2	0.8	0.12	0.8	0.12
14	0.7	0.2	0.8	0.2	0.8	0.2
21	0.8	0.2	0.8	0.15	0.8	0.1

TABLE VII

THE INFLUENCE OF TEMPERATURE UPON THE PRESERVATION OF A CHOLESTEROLIZED EXTRACT OF BEEF HEART

PRESERVATION DAYS	REFRIGERATOR 8° C.		ROOM (20° C.)		INCUBATOR (37° C.)	
	ANTICOMPL. 1:10	ANTIGENIC 1:100	ANTICOMPL. 1:10	ANTIGENIC 1:100	ANTICOMPL. 1:10	ANTIGENIC 1:100
1	0.6	0.2	0.6	0.2	0.6	0.15
7	0.6	0.2	0.5	0.2	0.5	0.2
14	0.7	0.2	0.6	0.2	0.6	0.1
21	0.6	0.2	0.6	0.08	0.7	0.1

TABLE VIII

THE INFLUENCE OF TEMPERATURE UPON THE PRESERVATION OF ACETONE INSOLUBLE LIPIDS

PRESERVATION DAYS	REFRIGERATOR 8° C.		ROOM (20° C.)		INCUBATOR (37° C.)	
	ANTICOMPL. 1:10	ANTIGENIC 1:100	ANTICOMPL. 1:10	ANTIGENIC 1:100	ANTICOMPL. 1:10	ANTIGENIC 1:100
1	0.8	0.4	0.8	0.4	0.8	0.4
7	0.8	0.4	0.8	0.5	0.8	0.4
14	0.6	0.4	0.5	0.4	0.5	0.4
21	0.6	0.3	0.5	0.25	0.6	0.12

in an incubator at 37° C. tend to lose slightly in antigenic activity as compared with portions kept in a refrigerator at 8° C. The maximum decrease in antigenic activity of extracts kept at 38° C. occurs during the first week; after that time the differences in antigenic activity are very slight or do not occur at all.

Extracts kept at room temperature (20° to 22° C.) occasionally show a slight decrease in antigenic activity during the first week as compared with portions kept in a refrigerator at 8° C.

2. *Influence upon Anticomplementary Activity.*—The results of anticomplementary tests conducted with normal serum are shown in Tables VI, VII, VIII and IX.

Allowing for the variations due to differences in susceptibility of the guinea pig complement sera to the anticomplementary effects of antigens, all extracts kept well over the period of twenty-eight days with practically no change in anticomplementary activity; furthermore, *no differences were apparent in the anticomplementary activity of portions of the different extracts kept at 8°, 22° and 37° C.*

3. *Influence upon Hemolytic Activity.*—The results of titrations for hemolytic activity for sheep corpuscles are shown in Table X.

TABLE IX  
THE INFLUENCE OF TEMPERATURE UPON THE PRESERVATION OF ANTICOMPLEMENTARY  
ACTIVITY OF TISSUE EXTRACTS

EXTRACTS	KEPT AT 8° C. FOR DAYS							KEPT AT 22° C. FOR DAYS							KEPT AT 37° C. FOR DAYS						
	1	5	9	14	22	28		1	5	9	14	22	28		1	5	9	14	22	28	
	0.2*	0.2	0.2	0.2	0.2	0.2		0.2	0.3	0.2	0.2	0.2	0.2		0.2	0.3	0.2	0.2	0.2	0.3	
Plain alc. human heart	0.3	0.4	0.3	0.4	0.3	0.3		0.3	0.4	0.3	0.3	0.3	0.4		0.3	0.4	0.3	0.4	0.3	0.3	
Plain alc. beef heart	0.2	0.3	0.3	0.3	0.3	0.3		0.2	0.3	0.2	0.3	0.3	0.3		0.2	0.2	0.2	0.2	0.3	0.3	
Cholest. human heart	0.5	0.5	0.5	0.5	0.5	0.5		0.5	0.4	0.5	0.5	0.5	0.5		0.5	0.5	0.5	0.4	0.4	0.4	
Cholest. beef heart	—	—	—	—	—	0.2		—	—	—	0.3	0.3	0.2		—	—	—	0.2	0.3	0.2	
Acet. Insol. Lipoids	0.5	0.4	0.4	0.5	0.5	0.5		0.5	0.4	0.4	0.4	0.4	0.4		0.5	0.4	0.3	0.4	0.4	0.4	
Cholest. + Acet. Insol. Lip.																					

\*Smallest amount of 1:5 dilutions just causing beginning inhibition of hemolysis; — = no inhibition with 0.5 c.c. of 1:5 dilution (largest amount tested).

TABLE X  
THE INFLUENCE OF TEMPERATURE UPON THE PRESERVATION OF THE HEMOLYTIC ACTIVITY OF TISSUE EXTRACTS

EXTRACTS	KEPT AT 8° C. FOR DAYS							KEPT AT 22° C. FOR DAYS							KEPT AT 37° C. FOR DAYS						
	1	5	9	14	22	28		1	5	9	14	22	28		1	5	9	14	22	28	
	0.2*	0.2	0.2	0.2	0.1	0.1		0.2	0.2	0.2	0.2	0.1	0.2		0.2	0.2	0.2	0.2	0.1	0.1	
Plain alc. human heart	—	—	—	—	—	—		—	—	—	—	—	—		—	0.5	—	—	0.5	0.5	
Plain alc. beef heart	0.2	0.2	0.2	0.2	0.2	0.2		0.2	0.2	0.2	0.2	0.2	0.2		0.2	0.2	0.2	0.2	0.1	0.1	
Cholest. human heart	0.3	0.2	0.2	0.1	0.1	0.2		0.3	0.2	0.2	0.1	0.1	0.2		0.3	0.2	0.2	0.1	0.1	0.2	
Cholest. beef heart	0.1	0.1	0.1	0.1	0.1	0.1		0.1	0.1	0.1	0.1	0.1	0.1		0.1	0.1	0.1	0.1	0.1	0.1	
Acet. Insol. Lipoids	0.3	0.2	0.2	0.2	0.1	0.2		0.3	0.2	0.2	0.2	0.2	0.2		0.3	0.2	0.2	0.2	0.2	0.2	
Cholest. + Acet. Insol. Lip.																					

\*Smallest amounts of 1:5 dilutions producing slight hemolysis; — = not hemolytic in 0.5 c.c. of 1:5 dilution (maximum amount employed).



Allowing for slight variations in the resistance of corpuscles from different sheep employed in these experiments, the results have

TABLE XI

THE ANTIGENIC SENSITIVENESS OF SALINE EMULSIONS OF TISSUE EXTRACTS KEPT AT 8° C.

EXTRACTS	PRESERVED EMULSIONS					FRESH EMULSIONS			
	DURATION	0.1	0.02	0.004	0.0008	0.1	0.02	0.004	0.0008
Cholesterolized Alc. Ext. Beef Heart	1 day	4	4	1	—	4	4	1	—
	4 days	4	4	4	1	4	4	3	—
	1 week	4	4	—	—	4	3	—	—
	2 weeks	4	3	3	—	4	4	3	—
	3 weeks	4	4	4	—	4	4	3	—
	4 weeks	3	3	—	—	3	1	—	—
Plain Alc. Ext. Beef Heart	1 day	4	1	—	—	4	2	—	—
	4 days	4	4	1	—	4	4	—	—
	1 week	3	2	1	—	3	2	—	—
	2 weeks	4	3	1	—	4	4	2	—
	3 weeks	3	2	1	—	2	2	—	—
	4 weeks	0	0	0	0	0	0	0	0
Acetone Insoluble Lip- oids	1 day	4	4	—	—	4	4	—	—
	4 days	4	4	1	—	4	4	1	—
	1 week	4	4	1	—	4	4	1	—
	2 weeks	4	4	1	—	4	4	1	—
	3 weeks	0	0	0	0	0	0	0	0
	4 weeks	0	0	0	0	0	0	0	0
Acetone Insoluble Lip- oids + Cholesterin	1 day	4	4	—	—	4	3	—	—
	4 days	4	4	4	—	4	4	3	—
	1 week	4	4	4	—	4	4	3	—
	2 weeks	4	4	3	—	4	4	3	—
	3 weeks	3	2	2	—	3	3	—	—
	4 weeks	2	1	—	—	2	1	—	—

TABLE XII

THE ANTICOMPLEMENTARY AND HEMOLYTIC ACTIVITIES OF TISSUE EXTRACTS DILUTED WITH SALINE SOLUTION AND KEPT AT 8° C.

PRESER- VATION FOR DAYS	PLAIN HUMAN HEART		CHOLEST. HUMAN HEART		ACETONE INSOLUBLE LIPOIDS		LIPOIDS CHOLEST.	
	ANTI- COMPL.	HEMO- LYTIC	ANTI- COMPL.	HEMO- LYTIC	ANTI- COMPL.	HEMO- LYTIC	ANTI- COMPL.	HEMO- LYTIC
	1:10	1:5	1:10	1:5	1:10	1:5	1:10	1:5
Tested at once	0.7	0.4	0.6	—	0.6	—	0.7	—
1	0.7	0.3	0.7	0.5	0.6	—	0.7	—
4	0.6	0.3	0.5	0.4	0.5	—	0.5	—
7	0.5	0.4	0.5	0.5	0.4	0.5	0.5	0.5
14	0.5	0.3	0.3	0.5	0.3	0.5	0.4	0.5
21	0.5	0.3	0.3	0.4	0.3	0.5	0.4	0.4
28	0.5	0.3	0.3	0.4	0.3	—	0.4	—

shown that preservation of extracts at temperatures from 8° to 37° C. has practically no influence upon their hemolytic activity, except possibly upon plain or crude alcoholic extracts of human and beef heart, which appeared to become slightly more hemolytic when kept at 37° C. than at 8° C.

## Part 2

### THE INFLUENCE OF TEMPERATURE UPON THE PRESERVATION OF SALINE DILUTIONS OF ALCOHOLIC EXTRACTS OF TISSUES

The following extracts were diluted with physiologic saline solution in a *uniform manner* and kept at 8° C.:

Plain alcoholic extract of beef heart

Cholesterolized alcoholic extract of beef heart

Acetone insoluble lipoids of beef heart in 3 per cent solution in methyl alcohol

Acetone insoluble lipoids and cholesterin.<sup>1</sup>

These and freshly prepared emulsions of each extract were subjected to comparative titrations at intervals over a period of twenty-eight days.

1. *Influence upon Antigenic Activity.*—The results shown in Table XI were observed in a series of titrations at intervals of one to twenty-eight days in which fresh and preserved emulsions of each extract were used in doses of five antigenic units with amounts of heated syphilitic sera varying from 0.1 to 0.0008 c.c.

Since different syphilitic sera were employed for the titrations on the first, fourth, seventh days and so forth, the results are not comparative for these separate intervals, *but the antigenic activities of the fresh and preserved emulsion of each extract are strictly comparative on each of these days.*

Only minor and inconstant changes in antigenic sensitiveness took place; *apparently saline emulsions of various tissue extracts when kept in a refrigerator at 6° to 8° C. do not change in antigenic activity over a period of twenty-eight days.*

2. *Influence upon Anticomplementary and Hemolytic Activities.*—The anticomplementary units of freshly prepared 1:10 saline emulsions of the four extracts studied, varied from 0.6 to 0.7 c.c.; the hemolytic units of 1:5 emulsions were about 0.5 c.c.

The results of titrations at varying intervals of emulsions of the

four extracts kept at 8° C. are shown in Table XII and indicate the following:

1. That preserved saline emulsions are slightly more anticomplementary than freshly prepared emulsions, *experiments have shown that this is due to bacterial contamination.*

2. The hemolytic activity of preserved emulsions remains quite constant, the changes being quite slight, but occasionally indicating that they may acquire slightly increased hemolytic activity.

#### SUMMARY

1. Various alcoholic extracts of tissues preserved in an incubator at 37° C. and in a laboratory at 22° C. tend to lose slightly in antigenic activity, as compared with portions kept in a refrigerator at 6° to 8° C.

2. Practically no changes in the anticomplementary and hemolytic activities of various alcoholic extracts of tissues took place over a period of twenty-eight days in portions kept in an incubator at 37° C., in a room at 22° C. and in a refrigerator at 6° to 8° C. Plain alcoholic extracts of heart, however, acquired slightly greater hemolytic activity when preserved at 37° C.

3. Emulsions of various alcoholic extracts of tissues prepared with physiologic saline solution and kept in a refrigerator at 8° C., did not undergo any marked or constant changes in antigenic activity over a period of twenty-eight days.

4. The preserved emulsions of each extract however, tended to become more anticomplementary and slightly more hemolytic, as compared with freshly prepared emulsions, due largely to bacterial contamination.

#### CONCLUSIONS

1. Alcoholic extracts of tissues (antigens) for the Wassermann test are best preserved in a refrigerator or at room temperature.

2. Fresh emulsions prepared with physiologic saline solution in a uniform manner as required, are preferred in a standardized test to emulsions carried over from day to day in a refrigerator.

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- <sup>2</sup>Kolmer, J. A., and Rule, A.: Technic for the Titration of Tissue Extracts (Antigens). *Am. Jour. Syphilis* (in press).

# Abstract of Current Syphilis Literature

It is the purpose of this JOURNAL to review so far as possible all literature on syphilis as it appears in other medical periodicals and to present it in abstract form. Authors are requested to send abstracts or reprints of their papers to the Associate Editor, Dr. Grayson E. Tarkington, Dugan-Stuart Bldg., Hot Springs National Park, Ark.

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**Syphilis of the Medium and Smaller Arteries.**—Aldred Scott Warthin, Ann Arbor, Mich. New York Medical Journal, 1922, vol. cxv, p. 69.

Simple arteriosclerosis (hyaline thickening of the intima) of the medium and smaller arteries is more common in syphilitics than in nonsyphilitics. It is probably not due to the localization of spirochetes in the intima, but is of secondary origin (toxic or mechanical). Syphilitic periarteritis, panarteritis and arteritis obliterans of the smaller arteries occur in all cases of chronic and latent syphilis, in greater or less degree. Syphilitic mesaortitis is essentially a disease of the arterial vasa vasorum. Syphilitic lesions of the smaller arteries are always associated with localization of the infection in any organ or tissue. The lesions are rarely gummatous in character. Syphilitic mesarteritis occurs in the carotids, subclavians, iliacs, femorals, tibial and pulmonary arteries. It is usually of slight degree, and is found only on microscopical examination. Occasionally it expresses itself clinically as aneurysm of these arteries, or in circulatory disturbances due to obstruction of the arterial lumen. Syphilitic obliteration of the pulmonary arteries may lead to the production of Ayerza's disease (chronic cyanosis, polycythemia and splenomegaly). Clinical syphilis of the peripheral arteries of the extremities is more common in the legs and feet, manifesting itself in gangrene, perforating ulcer, sclerosing atrophy, or symmetrical gangrene simulating Raynaud's disease. Little is known of the occurrence of syphilitic lesions in the arteries of the arms. Syphilitic arteritis may be a cause of peptic ulcer, or pemphigus, localized ulcers, atrophy and various forms of dystrophy, due to disturbed circulation, as the result of partial or complete obstruction of the lumen of the affected artery. Syphilis of the smaller arteries and arterioles plays a very important part in paresis, tabes and cerebrospinal syphilis, and in the production of localized degenerations of brain and cord. Syphilis of the coronary arteries is also of clinical importance. In general, it may be stated that localized syphilis of the smallest arterioles is an essential part of the general pathology of chronic or latent syphilis.

**The Visceral Changes in Congenital Syphilis.**—J. Frank Fraser, New York. The Journal of the American Medical Association, 1921, vol. lxxvii, p. 1623.

The lesions described may all be found in congenital syphilis, but at times those which might well be regarded as pathognomonic of the disease may be absent. Osteochondritis of the long bones (not discussed here because it is a skeletal lesion), for example, was not present in a case in which spirochetes were demonstrated, and characteristic lesions were found in practically all of the visceral organs. In the majority of cases, however, there will be found some lesion, if not in one organ in another, which will be sufficiently characteristic to enable the pathologist to come to a definite conclusion even before he receives a report on the bacteriologic examination.

**A Study of the Relation of Treponema Pallidum to Lymphoid Tissues in Experimental Syphilis.**—Louise Pearce and Wade H. Brown, New York. The Journal of Experimental Medicine, 1922, vol. xxxv, p. 39.

A widespread dissemination of *Treponema pallidum* from a local focus of inoculation in the rabbit constantly occurs by way of the lymphatics. Spirochetes were regularly recovered from the satellite lymph nodes by animal inoculation after scrotal inoculation; they were present as early as 2 days, when no specific reaction was detected, and at later periods of from 5 to 61 days after inoculation. Other superficial nodes at remote sites such as the popliteals and with no syphilitic lesions in the drainage area have also been shown to harbor active organisms. Although spirochetes were found in relatively few of the lymph node emulsions, the orchitis resulting from their injection was of a rapidly progressive type with an incubation period but slightly longer than that produced by a testicular or skin nodule emulsion rich in spirochetes. It has been shown that a syphilitic infection is sufficiently established in the rabbit body within 48 hours after scrotal inoculation so that the primary lesion is no longer essential for its maintenance. Active treponemata survive in the popliteal lymph nodes for long periods of time and have been regularly recovered from them in cases of true latency. The lymph nodes, therefore, function as reservoirs of the organisms. The ability to recover the spirochetes from lymphoid tissue through successive generation is seen in the serial passage of lymph node emulsion to testicle during an 18 months' period. The persistence of spirochetes in lymphoid tissue irrespective of the presence or absence of syphilitic lesions is a characteristic and fundamental feature of syphilis of the rabbit. The existence of infection, therefore, may be demonstrated at any time by the recovery of spirochetes from the popliteal lymph nodes by animal inoculation. This fact is of great practical importance in the therapy of the infection and may be profitably utilized in determining the ultimate effect of a therapeutic agent. These experiments demonstrate that the disease is not confined to the site of local inoculation but that lymphogenous dissemination of treponemata regularly takes place and that during the course of this process organisms become localized in the lymph nodes and exist there indefinitely irrespective of the occurrence of manifestations of dis-

case. The intimate relation of *Treponema pallidum* to lymphoid tissue is an essential concept of the rabbit, and from this point of view, the infection is primarily one of lymphoid tissue.

**Itching in Syphilis.**—Walter J. Highman, New York. *Archives of Dermatology and Syphilology*, 1922, vol. v, p. 63.

The outstanding features of this report are the negative history, the negative serum test, the atypical character of the lesions, and above all their itching. Every fact negated the likelihood of syphilis, including the minute anatomy of the lesions, and only the therapeutic diagnostic procedure, with provocation of the Wassermann test, finally solved the problem. Without precisely seeing how the error in diagnosis could have been avoided, considering the misleading data, the authors cannot entirely relinquish the thought that it was the belief that itching almost precluded syphilis that most surely dulled clinical astuteness. Phineas Abraham mentions that scrotal lesions may itch. The case herein reported supports the British writer's statement. Furthermore, it was a pure syphilide, one uncomplicated by any other itching dermatosis. Early syphilis is often seen in conjunction with scabies, and undoubtedly coexists with many other itching eruptions. In such an event, it is rarely difficult to make a correct clinical distinction between the two elements in the picture. But it is important to realize that certain syphilides themselves itch.

**Subcutaneous Fibroid Syphilomas of Elbows and Knees.**—Howard Fox, New York. *Archives of Dermatology and Syphilology*, 1922, vol. v, p. 198.

A rare manifestation of late syphilis is described in the case of a negress, aged 45. Undoubted evidence of syphilis was shown by a circinate group of nodules on one arm and the four-plus Wassermann reaction. On both elbows and knees were extremely hard, painless, subcutaneous nodules which appeared two years previously and remained unchanged during this time. They had no apparent relation to the bursæ. A histologic examination of one of the lesions showed a dense fibrous gumma. Two other similar cases from the literature are quoted at some length. The similarity of juxtaarticular nodules is discussed.

**Primary Syphilitic Nose Infection: Report of a Case.**—Kurt Jaenicke, Clinton, Ohio. *The Journal of the American Medical Association*, 1921, vol. lxxvii, p. 1889.

T. R., a man, aged thirty-five, married, whose family history was negative, who denied all previous venereal disease and who appeared healthy and robust, in August, 1921, while at work, was accidentally struck on the nose by a fellow laborer's shoulder. Slight tumefaction followed. About one month later he noticed a fissure at the entrance of the left naris extending from the ala inward toward the septum. A rhinologist cauterized the wound several times with chemicals in an effort to stay its progress, but the fissure steadily enlarged until a distinct ulcer was formed. When the patient came under observation, there

was an erosive sore on the floor of the left anterior naris about 1 cm. (three-eighths inch) long, 0.5 cm. (three-sixteenths inch) wide, and 4 mm. (five-thirty-seconds inch) deep, with a clean base and sharply elevated edges. The ulcer encroached on the skin of the upper lip to the extent of 2 mm. (eight-one hundredths inch). The neighboring tissues were indurated, and the submaxillary glands of the left side were moderately swollen. There was also a beginning papular syphiloderm sparsely scattered over the trunk and the legs. The patient's blood gave a four-plus Wassermann reaction. The manner of infection was probably from an intermediate source, the injury to the nose furnishing a fertile soil.

**The Existence of Gastric Ulcer with Tabes Dorsalis.**—B. B. Crohn, New York. The Journal of the American Medical Association, 1921, vol. lxxvii, p. 2023.

Three cases were discussed. The first was one of violent tabetic crises with symptoms very suggestive of gastric ulcer, but one in which the existence of the latter complication could not be established. The second was a case of tabes with predominant gastric symptoms and an apparent duodenal ulcer. The third was an example of advanced tabes with vomiting, hematemesis and melena due to an active bleeding duodenal ulcer. The frequency with which ulcer coexists with tabes cannot be stated. That it can so coexist and probably frequently does is most likely. The pathogenesis of the ulcer as a complication of, or as a coincident of tabes is probably as follows: Cerebrospinal syphilis is accompanied in a large percentage of cases by gastric hypersecretion. Organic lesions of the spinal cord or brain often cause delayed gastric motility, and probably abdominal gastric peristalsis. These two conditions presumably predispose to gastric or duodenal ulcer. Syphilitic aortitis may also play a rôle. Such ulcers as form are probably simple peptic and not syphilitic ulcers or syphilis of the stomach. The point of origin of the secretory and motor disturbances in the stomach and intestine is probably in the involvement in the pathologic process of the sympathetic fibers to these viscera in their passage through the dorsal spinal ganglions and posterior nerve roots. It is quite possible that the finding of a gastric or duodenal ulcer in tabes is a pure coincidence, and that there is no relationship of cause and effect between the two conditions.

**Syphilis and High Blood Pressure.**—Burton Peter Thom, New York. Medical Record, 1922, vol. ci, p. 89.

The author presents a protocol of the blood pressure measurements of fifty syphilitics from his service in the municipal prisons of the city of New York. Of these, twenty-five were women and twenty-five were men. The Wassermann reaction registered four-plus in all of them. In none of them were there any noticeable cardiac or renal lesions as evidenced by stethoscopic examination or urinalysis. All of them were selected at random. Of the twenty-five women only two, or 8 per cent, could recall the date of infection. This is in accord with the experience of most syphilologists and clinicians generally. Of the twenty-five men, only five, or 20 per cent, were unable to recall the date of infection, the remainder all

had a very distinct recollection of the appearance of the primary lesion. This is in marked contrast to the experience of the women in whom only two, or 8 per cent, could recall the appearance of the chancre. It will also be noted that of the men, six, or 24 per cent, showed tertiary lesions as compared to none shown by the women. None of the women examined had reached an age when an increased pressure would be noticeable, the youngest being twenty-one years and the oldest thirty-nine years. However, if we consider a pressure of 110 systolic as normal for a woman of twenty years, it was observed that thirteen, or 52 per cent, were above the normal; and if we consider a diastolic pressure not exceeding fifty as normal, the same number and percentage registered above the normal. It will thus be seen that more than half of these asymptomatic syphilitic females showed an increased blood pressure. Of the men examined the oldest was forty-five and the youngest nineteen. It is thus seen that the age average of the two sexes shows very little difference. If we consider a pressure of 120 systolic as normal for a man of twenty years it was observed that sixteen, or 64 per cent, were above the normal; and if we consider a diastolic pressure not exceeding sixty as normal, the same number and percentage registered above the normal. It will thus be seen that high blood pressure is present in the men in an excess of 12 per cent over the women. The number of women and the number of men showing an increased blood pressure total twenty-nine, or 58 per cent. Therefore it can be assumed that approximately one-half or more of all syphilitics, irrespective of sex or lack of objective symptoms, show an increased blood pressure.

**Sarcoid and Syphilis.**—Arthur William Stillians, Chicago. The Journal of the American Medical Association, 1921, vol. lxxvii, p. 1615.

Sarcoid of Boeck is a definite clinical type. There is no evidence that it can be caused by syphilis. Sarcoid of Darier-Roussy, if limited to those cases with roughly symmetrical lesions on the trunk, has not been shown to have been caused by syphilis. Sarcoid of the erythema-induratum-like type is sometimes caused by syphilis.

**Neurosyphilis With Negative Spinal Fluid.**—Harry C. Solomon, Boston, and Joseph V. Klauder, Philadelphia. The Journal of the American Medical Association, 1921, vol. lxxvii, p. 1701.

The authors' conviction is that there are many instances of active cerebral syphilis and even spinal syphilis in which the spinal fluid reactions are negative, but yet the patients are actively syphilitic and react favorably to anti-syphilitic treatment. Several cases were presented and discussed.

**The Early Manifestations of Syphilis of the Central Nervous System.**—E. M. Hammes, St. Paul. The Journal-Lancet, 1921, xli, p. 483.

A routine examination of the spinal fluid should be made in every case of syphilis. Treatment should be continued until the patient is not only free



from clinical manifestations, but until his blood and spinal fluid have become normal. With our present laboratory methods and clinical knowledge, syphilis can be diagnosed in its incipency, and, if properly and persistently treated, the grave degenerative forms can be reduced to the minimum.

**Report of Two Cases of Syphilis Simulating Epitheliomata.**—H. M. Robinson, Baltimore. Official Publication of the University of Maryland, 1921, vol. vi, p. 1.

A differential diagnosis of Gumma and Epithelioma:

Epithelioma (Basal Cell).

1. Occurs usually after 40 years.
2. No history of syphilis or accompanying symptoms or signs.
3. Usually on the face and head.
4. Pain slight, if any.
5. Discharge, small amount, often bloody.
6. Bleeds easily.
7. Edges of basal cell type are hard and indurated.
8. Very slow growth.

Gumma.

1. Occurs before 40 years of age.
2. Very often history of syphilis.
3. Usually on lower extremities.
4. Painless.
5. Discharge profuse and purulent.
6. Does not bleed easily.
7. Edges not indurated.
8. Moderately rapid growth.

**A New Method for Demonstrating Spirochetes by Lymph Gland Puncture.**—Irwin C. Sutton, Los Angeles. The Journal of the American Medical Association, 1921, vol. lxxvii, p. 1889.

Three minims of distilled water are drawn up into a Luer tuberculin syringe; a 24-gauge needle is then attached, the area over the satellite gland then painted with iodine, frozen with ethyl chloride, and the needle inserted until the gland moves with the needle. The needle is rotated several times and the plunger slowly withdrawn until 3 minims of serum are obtained. The mixture is then rapidly ejected into a small receptacle and redrawn into the syringe; this is done several times. A drop is taken and examined under the dark stage for the spirochete in the usual manner.

**Laboratory Findings in Early and Late Syphilis.**—John Fordyce and Isadore Rosen New York. The Journal of the American Medical Association, 1921, vol. lxxvii, p. 1696.

Not only is thorough investigation of every syphilis patient early in the disease recommended, but it is as imperative as the use of the dark-field in making an early diagnosis of the primary lesion. Although from the authors' analysis the percentage would seem higher, they do not believe that more than about 25 to 30 per cent of all secondary syphilitics show infection of the central nervous system. This can in the majority of cases be determined only with

certainly by a lumbar puncture, as in the early months clinical signs are often negligible; and to wait until the latter appear usually requires a longer time to bring about negative reactions. The authors' statistics show that the incidence of nervous system involvement is much higher in men than it is in women. The statement is frequently made that neurosyphilis has increased since the use of modern antisyphilitic remedies. This increase, in the opinion of the authors, is more apparent than real, and is to be attributed to the more systematic investigation of patients and our more thorough knowledge of the disease. The authors have no proof that arsphenamine adversely affects the optic, auditory or other cranial nerves. On the contrary, they have very definite data showing arrest of optic atrophy by the proper use of the drug. In considering the problem of neurosyphilis, one should always have in mind the general infection and especially the involvement by it of the cardiovascular apparatus and the eye. A persistent negative Wassermann reaction in the blood is frequently found with positive phases in the fluid and with an active process. A patient should never be discharged as cured without the information gained by lumbar puncture. When this has been neglected, it has in many cases led to disastrous consequences and incurable conditions. Pupillary anomalies and cranial nerve paralysis are often pathognomonic and are always suggestive of nervous syphilis. In papillitis and optic neuritis occurring in early syphilis, vision may be normal with only slight narrowing of the fields. The necessity for routine ophthalmologic examination must, therefore, be emphasized so that the earliest changes may be detected before irreparable damage is done to the eye. The absence of clinical signs and symptoms does not exclude syphilis of the central nervous system. The classical signs and symptoms of tabes may occur with a negative blood and spinal fluid. Likewise, neurosyphilis of the vascular, gummatous and other types may present subjective and objective clinical symptoms with an excess of globulin only in the fluid. The colloidal gold reaction has been employed by the authors for six years. They consider it of great diagnostic and prognostic value. A luetic curve enables us with almost absolute certainty to exclude paresis. A paretic curve is always present in paresis in untreated cases, but may be encountered in meningovascular syphilis and may disappear under treatment. A paretic curve is also found in some types of early neurosyphilis, and disappears as the other phases become negative.

**The Effect of Heat on Complement-Fixing Antibodies.**—R. L. Kahn; S. R. Johnson, and A. G. Boyd, Lansing, Mich. *The Journal of Infectious Diseases*, 1921, vol. xxix, p. 639.

It was shown that thermal destruction of syphilitic complement-fixing substances is markedly influenced by the mode of fixation. When fixation was carried out for 1 hour at water-bath temperature, the heating of serum for 30 minutes at 56° C. showed in a total of 87 serums tested an average destruction of 32 per cent. When fixation was carried out for 4 hours at ice box tem-

perature, some serums showed a slight loss, others, no loss and still others, a considerable gain in antibody content, with the result that the average finding of the 87 serums tested represented a gain of 10 per cent. Heating syphilitic serums for 20 minutes at 62° C. gave an average of seventy-five per cent antibody destruction, with water-bath fixation, and 46 per cent, with ice box fixation. The type of antigen employed was also found to influence thermal destruction of these antibodies. Heating serums for 30 minutes at 56° C. showed either little antibody destruction or an apparent gain in antibody content with 2 alcoholic extract antigens and one cholesterinized antigen and ice box fixation, while even with this mode of fixation, considerable destruction was noted at this temperature and period when employing the Noguchi antigen. Finally, it was shown that complement-fixing antibodies obtained on protein or bacterial injections were comparatively thermostable. These antibodies were found to be capable of withstanding a temperature of 65° C. Temperatures of 70° C. and 75° C. showed varying degrees of antibody destruction—somewhat more so in the case of bacterial immune bodies than those obtained on protein injections. With regard to the effect of the mode of fixation on specific antibody destruction due to heating, no marked difference was observed between water-bath and ice box temperatures.

**Incidence of Positive Wassermann Reactions in Four Hundred and Eighty-four Supposedly Nonsyphilitic Patients.**—Robert A. Kilduffe, Pittsburgh. *Archives of Dermatology and Syphilology*, 1922, v, p. 207.

The results of 567 Wassermann tests on 484 unselected patients admitted to hospital are reported, with some discussion of the findings. In 201 cases of pregnancy, one positive reaction with cord blood reaction corroborated by a positive reaction in the blood of the mother occurred an incidence of 0.5 per cent. Nine positive reactions in the cord blood alone were obtained. In 283 cases presenting miscellaneous medical and surgical conditions, forty-seven positive reactions occurred, an incidence of 6 per cent. In the 494 cases of the entire series, approximately 12 per cent of positive reactions were obtained; in twenty of the fifty-seven cases in which the patients reacted positively, there were either clinical or historical findings to corroborate the results of the Wassermann test.

**The Globulin Content of the Blood Serum in Syphilis.**—Max E. Bircher and Albert McFarland, Rochester, Minn. *Archives of Dermatology and Syphilology*, 1922, vol. v, p. 215.

In the majority of cases studied in which a high globulin content was present, it was found that this value decreased with the administration of each arsphenamine injection. Because of the limitations of space, it seemed unnecessary to tabulate each case, but tables are given as typical examples of this decrease in globulin, under treatment. The viscosity of the blood, based on 174 determinations in persons known to be syphilitic was usually found to

lie between 1.70 and 1.90. The lowest rate observed was 1.60 and the highest 2.05. The average was 1.79. These determinations were made before, during, and after treatment with arsphenamine. An endeavor was made to determine whether or not there was any relation between the clinical type of untreated syphilis and the viscosity. The untreated patients have been classified under three general clinical groups, and the average viscosity calculated. The viscosity in primary and secondary syphilis was 1.86, in tertiary syphilis, 1.83, and in syphilis of the central nervous system 1.82. The viscosity in untreated patients is perhaps a little higher than the average, but hardly enough to be of much significance. As to the relation between the clinical types and the viscosity, nothing can be deduced. Accepting as the average the viscosity of normal blood, the authors concluded that the blood viscosity in itself is of little significance in cases of syphilis either as an aid to diagnosis or to differentiation of clinical types.

**The Sachs-Georgi Reaction in Neurosyphilis.**—S. A. Levinson and W. F. Petersen, Chicago. *The Journal of Nervous and Mental Disease*, 1921 vol. liv, p. 413.

In an examination of the serum or the spinal fluid of 100 cases of neurosyphilis (tabes, paresis, cerebrospinal syphilis, etc.) an agreement of 78 per cent was found between the Wassermann and the Sachs-Georgi reaction. In 18 cases the Wassermann reaction was negative and the Sachs-Georgi reaction positive. In view of the extreme simplicity of the Sachs-Georgi reaction as contrasted with the Wassermann reaction, the authors are of the opinion that it offers a valuable aid in the diagnosis of neurosyphilis, used alone or as a control of the Wassermann reaction and supplementing it.

**A Preliminary Report on a Method of Determining the Number of Complement Binding Units in Sera Giving Positive Wassermann Reactions.**—Archibald McNeil, New York. *The Journal of Laboratory and Clinical Medicine*, 1921, vol. vii, p. 109.

In cases where there are a large number of complement binding units present in the blood when treatment is begun, the regular Wassermann test may show continuously four-plus reactions for a period of weeks or even months, whereas the titration method may show a continuous decrease in the number of complement binding units as the treatment progresses and the patient does not become discouraged and either discontinue treatment altogether or drift from one physician to another as so often happens. In a more detailed report on the titration method of performing the Wassermann test, a special study will be made of the so-called "Wassermann fast" cases, with regard to the possibility that they are in the majority of instances, simply cases in which the treponemata are immune to the drug or drugs that have been administered for a considerable period of time. Experimental work is at present being carried on to see whether it is possible by the titration method to determine

when the treponemata in any given case have become immune to a certain drug or drugs and when a change in treatment is indicated. Another interesting study that is being carried out by the titration method, is to determine the number of hours in which a single dose of the various drugs that are used in the treatment of lues will show their maximum effect on the Wassermann reaction.

**The Velocity of Fixation of Complement in the Wassermann Test.**—R. L. Kahn and R. M. Olin, Jr., Lansing, Mich. *The Journal of Infectious Diseases*, 1921, vol. xxix, p. 630.

The velocity of fixation of complement employing syphilitic serums and 6 different Wassermann antigens was studied. The periods of fixation were 0, 5, 15, and 30 minutes and 1, 2, 3, 4, 5, 6 and frequently 7 hours. The temperatures of fixation were bath, room and ice box, and, in some cases, water-bath and ice box. It was observed that the velocity of fixation of complement is not markedly affected by temperatures ranging between water-bath and ice box. The tendency for slightly stronger fixation at ice box temperature compared with that of the water-bath was noted with all antigens, except the Noguchi. The latter antigen showed a tendency for somewhat stronger fixation at water-bath temperature. It was also observed that a fixation period of 4 hours at ice box temperature approaches the maximum amount of fixation of complement with all antigens, including the Noguchi, although the latter in a few cases showed slightly more fixation after 1 hour in the water-bath than after 4 hours in the ice box. Finally, it was shown that the velocity of fixation of complement is directly proportioned to the concentration of antibodies in the syphilitic serums.

**A Rational Method of Producing Antihuman Amboceptor in Rabbits.**—George F. Klugh, Atlanta, Ga. *Southern Medical Journal*, 1921, vol. xiv, p. 684.

The author's method of producing antihuman amboceptor in rabbits is as follows: Select healthy young rabbits, about grown, males are preferable to females, since this eliminates pregnancy. Wash human cells until free of albumin and dilute cells to be used to 5 c.c. with sterile normal salt solution. Injections are given in marginal ear vein with 21-gauge needle. For the first injection use 1 c.c. of packed cells; second injection seventh day, 1 c.c. packed cells; third injection, fourteenth day, 0.5 c.c. of packed cells; fourth injection, twenty-first day, 0.5 c.c. packed cells. Test bleedings for amboceptor titration should be made on the twenty-first day before giving the fourth injection. This last injection is usually not necessary as amboceptor has been made by the anaphylactic reaction of the third dose. If amboceptor is not satisfactory one week after the fourth injection, it is useless to give further injections. The second dose seems unnecessary, but no time is lost by giving it, and doses one week apart allow ample time for sensitization before the third dose is given on the fourteenth day.

**The Significance of Biologic Reactions in Syphilis of the Central Nervous System.**—David J. Kaliski and Israel Strauss, New York. *Archives of Neurology and Psychiatry*, 1922, vol. vii, p. 98.

A review of the literature on the treatment of syphilis of the central nervous system has shown a growing tendency in this country to restrict intraspinal treatment to very narrow limits, which has been largely due to the efforts of Sachs and his associates. In Europe, with few exceptions, there has been a general abandonment of intraspinal methods. The former opinion of the authors which they still hold, of the very limited value of intraspinal treatment was based on these facts: The amount of arsenic present in autoarsphenamized serum was infinitesimal and of no spirocheticidal value. There was no valid proof that arsphenamized serum was in itself spirocheticidal *in vivo*. It was impossible to reinforce blood serum with more than an infinitesimal amount of arsphenamine. The introduction directly into the cerebrospinal fluid of any of the arsenical preparations was often dangerous and occasionally exceedingly painful. When nontoxic quantities were used the remedy was impotent. The pathologic changes in the various types of syphilis of the central nervous system are rarely only superficial, and are not reached by injection into the subarachnoid space. The method was physiologically wrong. Nutrition of the cerebrospinal tissues is not afforded by the cerebrospinal fluid which serves as an hydrostatic agent for the suspension of the brain and cord and an avenue of excretion. Therefore, medication of the nervous tissues via the cerebrospinal fluid was impossible. Substances introduced into the cerebrospinal fluid are rapidly absorbed into the blood and rarely diffuse through the subarachnoid space. The direction of flow in the so-called perineuronal lymph space is away from the nervous tissue toward the cerebrospinal fluid. The pressure in the cerebral capillaries is greater than that of the cerebrospinal fluid, so that fluid leaves the capillaries rich in material circulating in the blood, circulates in the pericapillary and perineuronal spaces, yielding nourishment and receiving waste matter, and finally leaves the tissues by the pericapillary and perivascular spaces to the subarachnoid cavities over the surface. Arsenic injected intravenously regularly reached the cerebrospinal fluid in greater quantities than could possibly be injected intraspinally without damaging or destroying the nervous tissue. This is true also of mercury and iodids. If the meninges are the seat of an acute or chronic inflammation, "antibodies" circulating in the blood stream reach the subarachnoid space. Intraspinal injections may serve to irritate the secreting mechanism and thus render it more permeable. Spinal drainage may act in a similar manner, as well as the reduction of fluid pressure.

**The Treatment of Syphilis by Mercury Inhalations.**—H. N. Cole, A. J. Geriecke and Torald Sollman, Cleveland. *Archives of Dermatology and Syphilology*, 1922, vol. v, p. 18.

Inhalations and fumigations of mercury have been tried at various times, since the earliest days of the appearance of syphilis in Europe. They have

always been abandoned as of uncertain efficiency, and occasional high toxicity. None of the methods so far proposed contain essential improvements over these antiquated methods. The unsatisfactory results are due mainly to the uncertain dosage. Local injury to the lungs is an additional factor. The assumption that mercury would be more promptly absorbed by the lungs was based on physical misconceptions. In fact the mercury is condensed on the mucous membranes of the mouth, pharynx, and respiratory tract. That in the mouth and pharynx is, for the most part, swallowed. The absorption then takes place by the gradual conversion of the mercury into soluble compounds just as it does with the ordinary administration of "gray powder." An improved technic was devised to insure the complete inhalation of definite doses of mercury or calomel, equivalent to those used in intramuscular injection. This was applied to a series of patients with active syphilis, but without any therapeutic or other systemic response. Larger doses appeared unjustifiable. Calomel produced objectionable local irritation. The results indicate that the administration of mercury compounds by inhalation has no advantage over oral administration; but, on the contrary, it has the serious disadvantage of indefinite dosage, and the consequent difficulty of steering between inefficiency and danger, and of special danger of respiratory irritation.

**A Contribution to the Mercurial Therapie of Syphilis.**—L. G. Hadjopoulos, Reginald Burbank and L. P. Kyrides, New York. *New York Medical Journal*, 1921, vol. cxiv, p. 596.

In the authors' opinion, in primary infections, salvarsan alone can accomplish the work, and, together with mercury, can manage advantageously the secondaries. Beginning with tertiaries, mercury takes the lead, with salvarsan as adjuvant in active, and probably alone in latent nonsymptomatic luetics. In other words, in arsenic and mercury we possess two valuable drugs acting on lues from its two extreme clinical stages; where one manifests its maximum efficiency the other is at its minimum with an intersection of their therapeutic intensities in late secondaries and early tertiaries. There is, however, a marked difference: salvarsan can eradicate the disease at its primary stage; mercury can only subdue it in its tertiary form. Attention is called to the fact that it is the synthetic arsenic 606 and not arsenic *per se* that accomplishes the cure in primary cases.

**The Clean Inunction Treatment of Syphilis with Mercury.**—H. N. Cole, A. J. Gericke, Torald Sollman, Cleveland. *Journal of the American Medical Association*, 1921, vol. lxxvii, p. 2022.

In treating syphilis by means of mercurial inunctions, probably the only mercury absorbed is that part of the mercurial ointment which is rubbed into the hair follicles, and entrances of the sebaceous and sweat glands. Hence, all superfluous ointment remaining on the skin may be cleansed off immediately after the inunction without lessening the mercurial effect. From forty-

four clinical cases of syphilis treated by this technic, they feel that they have been able to prove this clinically. As a result of their findings they feel that, in the future, mercurial inunctions need not be discarded because of the unpleasant considerations in regard to their use, namely, uncleanness, liability of discovery, and causing of a folliculitis. Mercurial inunctions following the technic that they advise are to be recommended in the treatment of syphilis as a distinct advance in the therapy of this disease.

**The Effect of Treatment for Syphilis on Severe Anemias.**—H. O. Fougar and John H. Stokes, Rochester, Minn. *The American Journal of the Medical Sciences*, 1921, vol. clxii, p. 633.

Severe anemia either primary or secondary, associated with late or latent syphilis, is apparently rare, twenty-five cases appearing in approximately 4800 records in the Section on Dermatology and Syphilology in the Mayo Clinic. Pernicious anemia may be seen in association with syphilis, but no case exhibiting an incontestable etiologic connection has appeared in the author's records. One patient with the clinical picture of pernicious anemia and a doubtful syphilitic infection has been apparently well two years as a result of treatment. Pernicious anemia in the apparent absence of syphilis may yield a positive serum Wassermann reaction. Mercury by inunction, used alone, produced an unfavorable reaction in four of nine patients with anemias who had previously improved under arsphenamine but all had primary anemia and subsequently showed evidences of a relapsing unfavorable course. The authors believe, therefore, that in syphilis with anemia mercury should be used with caution, especially if the picture suggests the primary type. Five of thirteen patients with primary anemia improved under arsphenamine. Of these two who improved and three who did not had demonstrable syphilis. Five of thirteen patients with primary anemia became worse under arsphenamine; of these two had syphilis. Five of twelve patients with secondary anemia improved under arsphenamine treatment. Of these only one who improved and five who did not had demonstrable syphilis. Only one of the twelve patients with secondary anemia became worse under arsphenamine. In the authors' experience arsphenamine has been much more effective in secondary anemia than in primary anemia, but curiously disappointing in secondary anemia with associated manifestations of syphilis. Twelve of sixteen patients improved under transfusion, four of them after arsphenamine had failed. Two of these patients showed only temporary improvement and three others died notwithstanding the improved blood picture. The effect of transfusion could only be judged with difficulty because of the conditions under which it was employed. In four of sixteen cases transfusion was without effect. Transfusion should be a preliminary to arsphenamine when the hemoglobin is below 20 per cent. Reactions to arsphenamine injections must be carefully avoided since they may produce an alarming drop in hemoglobin. No satisfactory rule for determining which case would improve on treatment for syphilis and which case



would not could be arrived at. In general half the cases may be expected to improve. The degree of improvement is not necessarily proportional to the demonstrability of syphilis. The pernicious anemia associated with undoubted syphilis which they have seen has run the ultimate course of pernicious anemia regardless of treatment for syphilis. Hemoglobin estimations alone are not sufficient to indicate the progress of the patient. The hemoglobin may rise and the number of erythrocytes fall at the same time. Arsphenamine treatment is safe if carefully used in anemia and should be employed in patients with undoubted evidence of the disease, and, as a therapeutic test, when reasonable suspicions of its presence exists. Transfusion must remain the ultimate resort in primary cases, and in those cases associated with syphilis in which arsphenamine has failed, even in the presence of syphilis, the best effect will be secured by both together.

**Treatment of Syphilis with Silver-Salvarsan.**—Victor G. Veeki, Millard R. Ottinger, San Francisco, Cal. *California State Journal of Medicine*, 1921, vol. xix, p. 438.

The authors started with an initial dose of 0.1 gm., and then increased to 0.2 gm., and finally to the maximal dose of 0.3 gm. From eight to twelve injections were given. They observed no untoward reaction of any kind in any of the patients. One patient who, after each of three injections of neosalvarsan, showed very pronounced and very disagreeable general and cutaneous reactions tolerated one small dose of silver-salvarsan very well. Results were uniformly good. Early syphilitic manifestations disappeared rapidly. One patient whose Wassermann reaction had remained positive in spite of two years' intensive antisyphilitic treatment, showed a negative reaction six weeks after twelve injections of silver-salvarsan. Another patient, with a somewhat mysterious and disfiguring facial syphilis, and who was previously treated in every possible way with slow but rather significant results, is rapidly improving and being made happy.

**Concerning the Therapeutic Value of Silver Arsphenamine.**—Oscar Berghausen, Cincinnati. *Medical Record*, 1921, vol. c, p. 944.

The patients all express a willingness to take another injection because no severe headaches nor gastrointestinal disturbances follow. Those who previously had been unable to take arsphenamine or neoarsphenamine without the production of symptoms, could readily take this newer preparation and suffer no ill effects. Improvement in the clinical condition was as marked as when the older preparation had been used. The Wassermann reaction, using both cholesterinized and plain alcoholic antigens and the method of ice box fixation, thus far has been determined in only twelve cases before and after the treatments. These results show that in 3 of the 12 it was possible to change the reaction from distinctly positive to negative, in 2 it was made less intense, and in 7 of the 12 or 58 per cent, it remained unchanged.

**A Preliminary Report on the Therapeutic Action of Silver Arsphenamine.—**

John A. Fordyce, New York. Archives of Dermatology and Syphilology, 1921, vol. iv, p. 737.

Silver arsphenamine is a valuable addition to our remedies for syphilis because of its greater freedom from reactions. The author's experience to date is too limited to warrant an opinion as to its superiority in effecting a cure. This can only be determined when we have standardized its employment and observed it over a longer period. At present the author feels justified in saying that it is as efficacious as the older remedies in causing cutaneous lesions to disappear, and his impression has been that in certain early cases it was perhaps more rapid in its action. The patients in whom negative reactions have been obtained have not as yet had a spinal fluid examination. Positive statements, therefore, cannot be made as to what the percentage of cures, with the dosage and intervals used by the author, will ultimately be. While some of the continental physicians are giving as high as 0.5 or 0.6 gm. at a dose, until we know more about the drug the author does not favor making the maximum dose at the present time greater than 0.3 gm.

**Intrarectal Administration of Salvarsan.**—Augusto S. Boyd and Morris Joseph, Panama. Proceedings of the Medical Association of the Isthmian Canal Zone, 1918, vol. xi, p. 77.

The intrarectal administration of salvarsan is a successful method of treating syphilis and relapsing fever. The untoward effects are practically eliminated by slower absorption. The method requires no special skill in administration, and can be entrusted to a nurse or the patient himself. The dosage can be increased by this route and it can be given as often as every 3 days. It is the method of choice in nervous subjects, obese or very anemic women and children. It offers at least the same curative value as the intravenous route.

**Report of Serious After-Effects of Arsphenamine Injections With Fatalities.—**

David A. Roth, Philadelphia. Proceedings of the Medical Association of the Isthmian Canal Zone, 1919, vol. xii, p. 20.

Inasmuch as serious untoward effects of arsphenamine were only observed when the drug was administered at comparatively short intervals, less frequent administration should be recommended to minimize the possibility of their occurrence.

**A Study of Silver Arsphenamine in the Treatment of Syphilis.—**

Mihran B. Parounagian, New York. The Journal of the American Medical Association, 1921, vol. lxxvii, p. 1706.

Silver arsphenamine of American manufacture has been administered 4,290 times to 756 patients. Clinical manifestations in all stages of syphilis have responded to treatment with silver arsphenamine with gratifying rapidity and

thoroughness. The author's impression is that response begins more promptly and that the lesions resolve with greater rapidity than is the case with a similar number of treatments with other arsenical preparations.

**The Synthesis of Arsphenamine and a Study of Some of Its Intermediate Derivatives.**—C. N. Myers, New York. *The Journal of Laboratory and Clinical Medicine*, 1922, vol. vii, p. 215.

The descriptions of the processes given show that there are three well defined methods by which "nitro oxy," the mother substance of arsphenamine, may be prepared. Attention has also been directed to the fact that the former, "nitro oxy," exhibits a peculiar type of dimorphism, which necessitates the exercise of extreme care in its preparation if the type best suited for reduction is to be obtained. Another important point which has been brought to notice is the importance of eliminating by-products from the intermediate substances notwithstanding the statements to the contrary made by some inexperienced investigators, who contend that these products will be removed at some later stage in the process. The foregoing descriptions of processes of manufacture have shown further that there are two well-defined procedures for reducing "nitro oxy" to arsphenamine base, namely, the progressive and direct methods. It may also be stated that it is the latter method, or some modification thereof, which is usually followed in the preparation of arsphenamine on a commercial scale. The modification most commonly made consists in the addition of magnesium chloride to the "hydrosulphite" mixture for the purpose of guarding against overreduction and sulphur compounds. A method for converting the free base into the dihydrochloride of arsphenamine has also been described. It should be stated here, however, that the process is not so simple as it appears at first glance, and that the exact technic followed in commercial practice is more or less known only to the manufacturers. It may be said in addition that the care exercised at this point is an important factor influencing the purity of the final product. "Hydrosulphite" contains metallic zinc and other inorganic impurities, which may be filtered off simultaneously with the free base and subsequently dissolved in the methyl alcohol-hydrochloric acid mixture if the proper precautions are not observed. With respect to the toxicity of the preparations on the market at the present time, it may be said that the average American product is somewhat less toxic than that which was formerly produced by German manufacturers. Occasionally, however, even the American product exhibits an abnormal toxicity as shown by the routine tests on animals. This is probably due to the presence of physical conditions which have not been definitely determined to date. The results of the toxicity studies described, however, are evidence to the effect that it is not due in any appreciable degree to the presence of arsenoxide, methyl alcohol, or the following intermediates and by-products: 3-amino-4-hydroxyphenylarsinic acid, oxalyl-4-aminophenylarsinic acid, 3-nitro-4-aminophenylarsinic acid, 3:5-dinitro-4-hydroxy-phenylarsinic acid, 3:5-dinitro-amino-

phenylarsinic acid. Arsenoxide, although 6 to 7 times as toxic as arsphenamine has been found in such small quantities (0.4 to 3.0 per cent) that it can hardly be considered an important factor in this connection. Furthermore the toxicity tests carried out indicate that there is no noticeable relationship between the degree of toxicity of arsphenamine and its "arsenoxide" content. Determinations made of the methyl alcohol content show that it is also present in such small quantities that it is a negligible factor. With one possible exception, 3-nitro-4-aminophenylarsinic acid, the intermediates mentioned are less toxic than arsphenamine. The variations observed in the hydrogen-ion concentrations of solutions of commercial samples of arsphenamine prepared by different manufacturers, using a fixed amount of alkali, indicate that the hydrochloric acid content may be a factor influencing toxicity. Animal experimentation in this field however, will be necessary before accurate conclusions can be drawn.

**Suggestion for the Avoidance of the Wassermann-fast State in the Treatment of Chronic Syphilis.**—Archibald McNeil, New York. The Journal of the American Medical Association, 1921, vol. lxxvii, p. 1970.

By using a modification of the usual technic of the routine Wassermann test, it is possible to measure in number of complement-binding units the power of any positive serum to bind complement and to demonstrate the effect any drug may have on this power. Briefly, the modification of technic consists in a very exact method of standardizing the complement and in the use of serial dilutions of the serum to be tested so that the result of each dilution differs from that of the preceding by just one-plus. By this means it is possible to make a series of titrations of the same serum, using different hemolytic systems, with practically uniform results. When the number of complement-binding units in the serum of a patient remains stationary under intensive treatment or is increased, it would seem safe to conclude that the spirochetes have become immune to the drug or drugs that are being administered; the patient, in other words is "Wassermann-fast" and will remain so until the treatment is changed to a more effective one. The serum of such a patient may have a complement-binding power equivalent to forty or more plus, which means that if the serum is diluted ten or more times with salt solution, the routine Wassermann test still gives a four-plus reaction. While the treatment continues effective, the serum of such a patient will give a more or less rapid decrease in the number of complement-binding units; but as soon as the spirochetes become immune to the treatment, the number of complement-binding units, for a while may remain practically stationary, and if the treatment is continued the number of units may increase to almost the same extent as if no treatment whatever was given. When the treatment is changed, however, the spirochetes may again be attacked, and the number of complement-binding units usually show a decrease after each treatment until the spirochetes, according to the theory, again become immune to the drug that is being given. The author's experience indicates that when the comple-

ment-binding units of the serum show no further decrease after three successive treatments, the case is "Wassermann-fast" so far as that form of treatment is concerned. It seems, furthermore, that a prolonged treatment with any single drug or combination of drugs is likely to result eventually in the establishment of this resistant state, thus causing injury to the patient and a serious loss of time in effective treatment. As the number of therapeutic agents that affect spirochetes are few, it would seem wiser to administer only one at a time so that when the spirochetes become immune to one it may be replaced by another drug to which they are not immune.

**Treatment of Syphilis as Carried Out in the Vanderbilt Clinic, New York City.**

—David S. Grim, New York. Proceedings of The Medical Association of the Isthmian Canal Zone, 1918, vol. xi, p. 64.

In the early primary stage the diagnosis is established by finding the *Spirocheta pallida*. A physical examination, including a urine examination, is made, when the patient receives at once 0.4 gm. arsphenamine intravenously. The patient returns the following day and receives gr. one to one and one-half, mercury salicylate injected into the gluteus maximus. The patient returns to clinic three times a week for 0.4 gm. arsphenamine, intravenously, until 8 or 10 doses have been given; and every 5 days for an intramuscular injection of mercury salicylate, grs. one to one and one-half until 12 injections have been given. This constitutes the first course. The patient is given a rest from treatment for 6 or 7 weeks, when the second course is begun. The blood Wassermann is taken before the second course is begun. During the second course the patient receives about 0.5 gm. arsphenamine intravenously every 4 or 5 days until about 10 injections have been given, and one to one and one-half gr. mercury salicylate intramuscularly every 5 days until 12 doses have been given. In all probability the case is cured. The Wassermann test is employed as a control and subsequent treatment is administered only if indicated. In the secondary stage, treatment is not so intensive. Mercury salicylate gr. one to one and one-half is given intramuscularly. The patient is ordered a cathartic and placed on restricted diet. The following day he receives 0.3 gm. arsphenamine intravenously. This is repeated three times a week until 8 to 10 injections have been given. The mercury is given every 5 days until 12 injections have been given. The Wassermann test is then made which is usually found to be negative, but generally it will not remain negative. After a rest from treatment for 5 or 6 weeks the second course similar to the first is given, after which the case is probably cured. Every secondary case receives a spinal puncture and an examination of the spinal fluid. In the tertiary stage arsphenamine is given in doses of 0.4 to 0.6 gm. at slightly longer intervals for 8 to 10 doses, always intravenously. Mercury salicylate in doses of gr. one to one and one-half is given intramuscularly every 5 days for 12 doses. Periods of rest follow each course. The number of courses is controlled by the Wassermann findings and the clinical condition of the patient. It is much more difficult to obtain a serological cure in the advanced

stages than in the earlier types. Potassium iodide is frequently found very helpful in the later stages. Local conditions receive local treatment as indicated. Reverting to the spinal fluid examination in the secondary stage, if there is present a pleocytosis, an increase in globulin, a Wassermann and colloidal gold test positive to 1 or 2 c.c. of fluid, persistent, thorough intravenous and intramuscular treatment may permanently restore the spinal fluid to normal. If, however, such treatment has made no impression on the spinal fluid reactions, and especially if the Wassermann and gold tests are positive to quantities of fluid down to 0.3 c.c., paresis or tabes can be looked for and intraspinal treatment in conjunction with the intravenous and intramuscular treatment always precedes intraspinal treatment, and in certain forms of cerebrospinal lues potassium iodide also is given before. Before a case of syphilis is finally pronounced cured, a provocative dose of arsphenamine, 0.4 gm., is administered intravenously. A series of blood Wassermann is then made at the end of 24, 48, 72 hours; 1 week; 10 days and 20 days. If these are negative the case is considered cured. Wassermann tests at intervals of 4 to 6 months for a period of 2 to 4 years are recommended.

**A Proposed Standard Treatment for Early Syphilis.**—George Walker, Baltimore, Md. *Southern Medical Journal*, 1921, vol. xiv, p. 683.

The author recognizes the fact that no really satisfactory standard treatment of syphilis will be possible with our present knowledge of certain drugs and their effect. A standard outline consisting of five courses is given. The first consists of seven intravenous injections of 0.6 gm. arsenobenzol at seven-day intervals, with seven injections of mercury salicylate in the buttocks. Thirty days rest is allowed. Course No. 2—Six intravenous injections of novarsenobenzol starting with 0.6 gm. and reaching 0.9 gm. on the third injection. Six injections of mercury salicylate are also given. Thirty days rest is then allowed. Course No. 3—Potassium iodide, saturated solution, twenty-five drops t.i.d. for thirty days. Course No. 4—Course No. 2 is repeated, then thirty days rest. Course No. 5 is of two months' duration, first month potassium iodide, as in course No. 3, and mercury salicylate one gr. intramuscularly at seven-day intervals for five doses. The second month is a repetition of course No. 2.

**The Treatment of Early Syphilis.**—C. Morton Smith, Boston. *Archives of Dermatology and Syphilology*, 1921, vol. iv, p. 723.

The minimum of treatment for a case of primary or early secondary syphilis should consist of: (1) mercurial dressings to initial lesions; (2) intravenous arsphenamine, 0.1 gm. to 40 pounds body weight, repeated in from 3 to 5 days, and then at five-day or weekly intervals until six to ten injections have been given; (3) full doses of mercury, preferably by intramuscular injection; if an insoluble salt, fifteen injections should constitute the first course, and (4) frequent examinations of the urine. Following the mercurial injections, an

interval of five or six weeks should elapse before checking up with the Wassermann test. If it is positive, the first course should be repeated. If negative, a vacation of three months is allowed, at the end of which time ten or twelve mercurial injections and from four to six of arsphenamine are given. With a second negative Wassermann reaction, during the following six months from six to eight mercurial injections are given, and during the next year the patient should receive short courses of mercury. An examination of the cerebrospinal fluid should be made early in the disease if possible and certainly before the patient is discharged. Patients with organic disease who acquire syphilis are treated with the same or greater consideration than patients showing the same sort of damaged organs of syphilitic origin.

**Therapy in Neurosyphilis, With Particular Reference to Intraspinal Therapy.—**

Walter F. Schaller and Henry G. Mehrtens, San Francisco. *Archives of Neurology and Psychiatry*, 1922, vol. vii, p. 89.

Intravenous and intramuscular therapy caused symptomatic improvement in the majority of cases. Serologically only 19 per cent cleared up entirely. It was more efficacious in the meningeal, vasculo-meningeal and diffuse types. Drainage, in addition to the foregoing results, impressed the authors as a definite advance both in ability to ameliorate symptoms and in tendency to improve the spinal fluid pathology. Intraspinal medication was superior to the intravenous and intramuscular methods in its effectiveness in clearing up the spinal fluid. Forty-eight per cent of the cases became clear through the use of the intraspinal methods as compared to 19 per cent following the intravenous method. The most useful field for intraspinal therapy is that of the meningoparenchymatous types, including tabes. However, patients with optic atrophy and with tabes without meningeal reaction received no benefit. Patients with parenchymatous lesions (including paresis) did poorly, but 25 per cent of the cases thus treated cleared up clinically and serologically. A remission, at least, was effected. In the authors' experience complications in intraspinal therapy are no more frequently met with than in intravenous medication. Massive rectal injections of neoarsphenamine (4 gm.) may be profitably substituted for arsphenamine given intravenously in intradural medication when intravenous injection is impracticable. In the treatment of the individual case of neurosyphilis, it would therefore seem proper to begin with intensive intravenous and intramuscular medication, particularly in vascular, meningovascular and diffuse lesions. Failure to reduce spinal fluid findings to negative after a thorough trial should suggest the advisability of using more intensive methods. Drainage, combined with intravenous injections, again should be the procedure of choice when the facilities for more complicated methods are lacking or when symptoms of increased spinal fluid pressure are distressing. The Swift-Ellis, Ogilvie or Byrnes method should be reserved for cases resistant to the foregoing efforts. These resistant cases will be found particularly in tabetic patients. Patients with optic atrophy and neurosyphilis without cerebrospinal fluid reaction receive no advantage from intraspinal medica-

tion. Parietic patients should be given a trial. Patients with inadequate veins can profitably receive the arsenic in the form of massive rectal injections of neocarsphenamine.

**Observations Following Intravenous Injection of Hypertonic Salt Solutions in Cases of Neurosyphilis.**—James Wynn, Boston. *Archives of Internal Medicine*, 1922, vol. xxix, p. 72.

Intravenous injections of 200 c.c. of 15 per cent salt solution were given to six patients with neurosyphilis, with resulting disagreeable but not alarming symptoms. In these cases the cerebrospinal fluid pressure was found to rise sharply and then to fall, reaching a point about 100 mm. below the original level by thirty minutes after the end of the salt injection. Salt injections were given according to a definite routine over a period of months, augmenting intraspinal treatment in a group of patients with neurosyphilis. There was no serologic or cytologic improvement over the usual course with intraspinal treatment alone, and symptoms were distinctly aggravated. Such injections hence would seem to have no therapeutic value in this group of neurosyphilis cases. In a short series of cases whole blood chlorids were determined before and at intervals after salt injections, the output of salt in the urine was ascertained, and blood pressures were followed; immediately after the intravenous injection of 200 c.c. of 15 per cent salt solution the average whole blood chlorid elevation above normal (i.e., the first determination) was 57 per cent; one hour later, 26 per cent; twelve hours later, 18 per cent. In from seventeen to twenty-two hours, about half of the injected salt had been excreted in the urine. Variations in blood pressure were within physiologic limits.

**The Treatment of Antenatal and Congenital Syphilis.**—John A. Fordyce and Isadore Rosen, New York. *Archives of Dermatology and Syphilology*, 1922, vol. v, p. 1.

Every prospective mother should receive a routine Wassermann examination. The proper treatment of a syphilitic mother during pregnancy will undoubtedly result in the birth of a healthy infant. Every infant born of a mother or father with syphilis should have a Wassermann test made at birth; and again two weeks later, then every four weeks up to six months, and after that every three months up to two years. If the reaction is negative with all these tests and no clinical signs have appeared, the baby in all probability escaped the infection. A certain number of infants born of mothers with strongly positive reactions give a positive cord reaction, but subsequently all tests are negative, and they fail to show any clinical manifestations of the infection. They should, however, be kept under observation for at least two years. Occasionally an infant with active clinical signs of syphilis will give negative serologic findings, usually only temporarily. The clinical diagnosis should always take the precedence over the laboratory diag-



nosis and proper treatment should be instituted. In the treatment of the authors' patients having congenital syphilis they have adopted as the method of choice the systematic intramuscular injection of neoarsphenamine and mercury. They not only have had good clinical results but also have been able to obtain negative reactions in fourteen of their infants out of a total of forty-seven with four-plus blood reactions, when the treatment was begun within the first few months. The authors believe that systematic treatment begun early, in the first week or two, where possible, will result in the clinical serologic cure of the infant.

**Intraspinal Treatment of Neurosyphilitic Patients.**—Grant Marthens, Dayton. The Ohio State Medical Journal, 1922, vol. xviii, p. 13.

All cases of neurosyphilis should receive the benefits of intensive intraspinal therapy. The incidence of improvements after treatment is greater than the ordinary remissions characteristic of paresis. Paretics show a greater degree of improvement after the administration of mercurialized serum than of fortified salvarsanized serum. Mercurialized serum seems to be contraindicated in tabo-paretics.

**Two Hundred and Fifteen Cases of Syphilis After Five Years.**—H. G. Irvine, Minneapolis. The Journal of the American Medical Association, 1921, vol. lxxvii, p. 1620.

Further studies of this kind on larger groups, if possible, should be made. Looking toward such studies, every effort should be made to keep accurate and detailed case histories. Patients receiving treatment for more than an ordinary length of time should pass through the hands of competent consultants to check carefully visceral syphilis and nerve involvement. The value of social service and personal contact in keeping patients under observation should be emphasized. Good medical service cannot be rendered if the patients do not attend the clinic. The author believes that this study, although limited, indicates that present accepted methods of treatment are adequate and, with the increased number of clinics with their better facilities, the increased educational activities and the new public health program, the outlook in this field is decidedly hopeful.

**The Treatment of Late Syphilis, and of Syphilis in Mother and Child.**—John H. Stokes, Rochester, Minn. Archives of Dermatology and Syphilology, 1921, vol. iv, p. 778.

This rather cursory review of the principles underlying certain special phases of syphilis will defeat its own purpose if it leaves the impression that the treatment of the disease should be parcelled out in segments, each self-sufficient and governed by its own laws. Just as we are finding that early syphilis is no longer localized, even at the earliest appearance of the primary lesion, so

we shall find as the intensity of our study increases that late syphilis does not begin in the first decade, but in the first hour. Preventing the transmission of the disease in its earlier stages, and forestalling the individual tendency to complications based on the peculiarities of the strain of parasite, the host, and the method of treatment, is the whole problem of syphilis. Forestalling implies detection, so that an increasing diagnostic alertness, a development of methods for detecting the earliest and not the late signs of pathologic change in vital organs and tissues, is not mere diagnosis, but a part of effective treatment. For all our so-called prophylactic effort, nothing will prevent the development of late complications in a certain group of patients who present the fatal combination of predisposed soil and trophic organism. It is equally true that an even smaller group of patients will master the infection for themselves, irrespective of our interference. Between these two extremes will come those whom we have radically cured, those whom we have managed to place in commensal relation to their infecting organism, those whose immunity we have broken by treatment measures whose potentialities for future harm as well as present good we do not yet understand, and those whom we have destroyed outright by treatment itself. The study of the interrelation of these groups is one of the most complex problems of medicine today. Its solution will not be accomplished by a mental or physical separation of the various phases of syphilis and syphilotherapy into air-tight compartments each with its own technic, ideals and aims. Only that mode of approach will leave a significant impress on our future knowledge which envisages the entire disease, employs one or two methods in a large series of cases over a period of many years, records the results, and which, by lifelong observation and periodic complete reexamination, detects impending serious pathologic change, and evaluates in detail and with accuracy the response of parasite and host.

## BOOK NOTICES

(Books for Review should be sent to Dr. W. H. Deaderick, Editor, Dugan-Stuart Bldg., Hot Springs, Arkansas.)

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**DISEASES OF THE SKIN AND THE ERUPTIVE FEVERS.**—By Jay Frank Schamberg, M.D., Professor of Dermatology and Syphilis, Graduate School of Medicine, University of Pennsylvania. Fourth Edition Thoroughly Revised. Octavo of 626 pages, 265 illustrations. Philadelphia and London: W. B. Saunders Company, 1921. Cloth, \$5.00 net.

The fourth edition has been revised, old chapters rewritten and new ones added. A separate chapter is devoted to the acute Eruptive Fevers which is adequately illustrated and complete in every detail. The chapter on syphilis has been rearranged and rewritten, fifty-five pages are devoted to the subject of which twenty-four deal with treatment alone. Treatment is discussed under five heads. Prophylactic treatment, abortive treatment, treatment of primary, secondary, and tertiary stages, treatment of neurosyphilis, treatment of congenital syphilis. The treatment of syphilis with the arsenobenzenes is fully discussed including the types and causes of arsphenamine reactions. The arrangement of the entire book is good and the book is well printed.

**DISEASES OF THE SKIN.**—By Henry W. Stelwagon, M.D. Ninth edition, revised with the assistance of Henry K. Gaskill, M.D., attending Dermatologist to the Philadelphia General Hospital. 1313 pages with 401 Text Illustrations and Half-tone Plates. Philadelphia and London: W. B. Saunders Company, 1921. Cloth, \$10.00 net.

The ninth edition of this work has been revised and now appears with 1313 pages and 401 text illustrations and half-tone plates. This work of revision was completed by Dr. Henry K. Gaskill, who was assisting Dr. Stelwagon in the preparation of the ninth edition. It is just twenty years since the first edition of Dr. Stelwagon's book

appeared, during this time it has frequently been revised and reprinted until at the present time it is one of the most exhaustive works on diseases of the skin obtainable. The first 127 pages are devoted to a consideration of the general anatomy and physiology of the skin, general symptomatology, etiology, diagnosis, treatment and classification. The classification followed by the author is the system of Hebra, with modification by Crocker. Particular attention is devoted to diagnosis and treatment. Seventy-six pages are devoted to the cutaneous manifestations of acquired and hereditary syphilis, practically every lesion in this section is illustrated. Sixteen pages are devoted to treatment of the syphilitic lesions. The methods described are in accord with the present day teachings. No library of either the general practitioner, or dermatologist is complete without this book.

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### Announcement

It shall be the future policy of THE AMERICAN JOURNAL OF SYPHILIS to make its pages of greater working value to a greater number of subscribers than in the past. To this end contributions dealing only with the practical or clinical aspects of syphilis will be solicited. Articles now in hand dealing with technical problems will be published. While the Journal is very grateful to all past contributors, this change of policy has been determined upon after numerous requests from subscribers.

# The American Journal of Syphilis

A QUARTERLY JOURNAL DEVOTED TO THE  
STUDY AND PREVENTION OF SYPHILIS

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Vol. VI.

St. Louis, JULY, 1922

No. 3

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## Original Articles

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### A STUDY OF 443 CASES OF HEREDITARY SYPHILIS WITH ESPECIAL REFERENCE TO RESULTS OF TREATMENT

#### PART I. SOCIAL AND CLINICAL DATA

BY DR. PARK J. WHITE AND DR. BORDEN VEEDER, ST. LOUIS, MO.

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Medicine. Aided by a grant from the Interdepartmental  
Social Hygiene Board.*

(Received for publication, June 6, 1922)

#### INTRODUCTION

SINCE the year 1912 hereditary syphilis has been the subject of special and intensive studies in the clinics associated with the Department of Pediatrics of the Washington University School of Medicine.<sup>1\*</sup> In addition to a number of members of the staff who have been interested in the subject, a special social worker has been employed since 1914 for following up syphilitic children, investigating the social problems, and carrying on the routine work of the long-continued treatment which is necessary for these cases. In 1918 the Interdepartmental Social Hygiene Bureau granted a sum of money

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\*For references, see Part II.

to reinvestigate these syphilitic children with a view to ascertaining as far as possible exactly how much had been accomplished and whether or not the results obtained by this intensive work lasting over a period of years were in any way commensurate with the time, effort, and money expended. It was felt that the problem had been attacked during this period with sufficient intensity to warrant a taking of stock, so to speak.

A social worker was obtained and one of the members of the staff (Dr. White) assigned to the research. A series of forms was prepared so as to record in a convenient way the social, clinical, and therapeutic data in regard to the progress of each case, and information gathered from the clinic, hospital, and social service records. Cases of known dead were closed with an analysis of the condition as last recorded and then an attempt was made to ferret out and re-examine clinically and serologically the living children. The total number of families in which one or more syphilitic children had been in attendance during this time was 396. The years during which the families came under observation were as follows:

1910—	2	1916—	68
1911—	2	1917—	62
1912—	26	1918—	36
1913—	50	1919—	34
1914—	54	1920—	1
1915—	60	1921—	1

Only two families observed later than 1919 were included (these for relationship with families previously studied) as the children admitted after 1919 had not been under observation or treatment long enough for the purposes of this study.

While it was the original intention of the research to consider only treatment and its result, so much social and clinical data were brought together during the investigation that it was decided briefly to present this additional material. For purposes of convenience the results of the investigation are divided into two sections: (1) social and clinical, (2) therapeutic. The material consists, as stated, of 396 families. From these 396 families 443 children were studied who were definitely syphilitic; 197 of the 443 were infants under two years of age and the remaining 246 children were first seen when in the stage of "late" hereditary syphilis. In all, over a year was required in reassembling data from old records, examining all

cases (164) which could be located, getting in touch with out-of-town cases (150), and searching vital statistics for cases (136) not accounted for or lost through faulty or misleading addresses. The social worker made 624 visits, obtaining definite information regarding 198 cases. Only 32 of the 150 out-of-town cases could be reached and the data used for closing the observations on these cases is the last information given in the records as to the condition. Sixty-five visits were made by Dr. White to patients in their homes where the social worker was unable to persuade the parents to bring the children to the hospital for reexamination. The above data are given in order to indicate the effort that was made to obtain a clear-cut picture of the patient at the time he was brought to the clinic with active disease, the further course, the treatment, the reaction to treatment, and finally the end result.

A number of investigations of the fate of syphilitic children have been made, but, with the exception of a report by Müller and Singer<sup>2</sup> published in 1918 which came to our notice after our work was nearly completed, these were in the pre-Wassermann and pre-salvarsan period. Among them may be mentioned the studies of Karcher<sup>3</sup> and of Pott<sup>4</sup> in 1901, of Hochsinger<sup>5</sup> in 1910, and Welde<sup>6</sup> in 1913. Müller and Singer report in detail the results obtained in the special department for syphilitic children in the Friederichs-Waisenhaus in Berlin. This department was established in 1909 for the care and treatment of syphilitic children over one year of age and consequently their results are difficult to compare with ours. In all, 202 syphilitic children passed through their hands during the nine years following the year 1909. Infants with syphilis were treated in another division and many of these 202 children had been treated before entering the special division. Of these 202 patients 46, or 22.8 per cent, died and 74 were lost or incompletely followed for one reason or another. Thus they found a difficulty similar to our own in following up and keeping track of syphilitic children even in a country where every individual and change of residence is recorded with the police department. Thirty-six of the 46 deaths took place in the institution as a result not only of the low resistance of the individual infected with syphilis, but of the constant, repeated exposure to other infectious diseases to which the institutional child is subjected. The remaining 82 cases are grouped by Müller and Singer into A (11 children) treated by mercury alone;

B (54 children) treated by mercury and salvarsan, but with treatment not as thorough or intensive as considered essential today; and C (17 children) treated thoroughly with calomel ointment and neosalvarsan courses. Their results will be considered later in connection with our data in regard to treatment.

#### SOME SOCIAL ASPECTS OF HEREDITARY SYPHILIS

There has been considerable discussion of the importance of syphilis from a social standpoint in recent years and a number of valuable contributions to the subject have been published discussing the familial aspects, the relation to infant mortality, syphilis as a cause of fetal death, and the like. In going over these papers, however, we find it impossible to group or compare statistics and to picture inherited syphilis as a whole because of the varied sources of material upon which the studies were based. Thus in the exceedingly interesting study of Solomon and Solomon<sup>7</sup> the start was made from the adult patient with a late central nervous lesion and their group of 555 families are thus of a limited class, as the authors recognize. In Jeans' earlier communication from our own clinic, as in our own, the start is made from the syphilitic child. Solomon and Solomon found that in 128 of their 555 families (23 per cent) pregnancy had not occurred and in 37 more (6.7 per cent) pregnancy had occurred but there were no living children, while in our own work only families with syphilitic children are included. This same use of restricted material makes it almost impossible to determine accurately the social importance of hereditary syphilis as an infectious disease, or with any degree of exactness to determine its extent, for, not only are we limited by the source of material—neurologic, obstetric, or pediatric clinic, but the nature of this material more or less limits the investigation to a certain social stratum. For these reasons we consider it more or less useless to review or more than incidentally to refer to other studies. Our own figures relate only to syphilis in families where one or more living syphilitic children have come under our observation.

Syphilis in the parents may react upon the succeeding generation in several ways: First, by preventing or inhibiting pregnancy; second, by causing the death of the unborn child; third, by being transmitted to the living child while yet in utero. As the first factor does not enter into our own material we shall mention it only



briefly for the sake of completeness. There is considerable difference in the figures for the percentage of sterile marriages depending upon whether one or both parents have syphilis. Raven<sup>8</sup> gives 9 per cent of syphilitic marriages as sterile, Haskell<sup>9</sup> 32.5 per cent, Heubner<sup>10</sup> 45.7 per cent, Regis<sup>11</sup> 75 per cent, Solomon and Solomon<sup>7</sup> 23 per cent in their group of 555 families. The exact importance, therefore, of syphilis as a factor in producing sterility must be considered undetermined, but the evidence seems to show that syphilis does increase the amount of sterility.

*Syphilis as a Factor in Producing Accidents to Pregnancy.*—As stated, our group consisted of 396 families in whom we found 443 syphilitic children. In 372 of these 396 families there had been 1,443 pregnancies. In 24 families it was impossible to obtain any accurate or definite information regarding the number of pregnancies.

Total number of pregnancies (272 families) . .	1,463
“ “ living births . . . . .	1,145
“ “ miscarriages and stillbirths . . .	318
Percentage of miscarriages and stillbirths . . .	21.7

That syphilis is a frequent cause of fetal death is of course well known. Jeans a few years ago collected the figures of twelve reports which gave a total of 30.3 per cent of fetal deaths in 4,148 pregnancies occurring in syphilitic families. The individual figures varied all the way from 17.2 per cent in the largest series to 62 per cent in the smallest. Our figure is considerably lower than Jeans' figure, but it is still twice as large as the figure of approximately 10 per cent for stillbirths and miscarriages among women of the same social condition in St. Louis when there is no obvious syphilis in the group. Solomon gives a figure almost identical with our own—there having occurred 297 accidents to pregnancy in 1,432 pregnancies, or 20.7 per cent, in his group of families with late syphilis. The importance of syphilis as a cause of fetal death is well illustrated in another way by the figures of Williams<sup>12</sup> from his obstetrical material. In 4,000 pregnancies there were 302 fetal deaths of which 102, or 34.4 per cent, were due to syphilis. Syphilis, according to Williams, ranks highest among the causes of fetal death. One may without exaggeration draw the conclusion that when syphilis is present in a family the chances are 1 in 5 of an

accident to pregnancy (stillbirths or miscarriages) as against 1 in 10 in families free from syphilis. But in connection with this must be recorded the fact that in 175 of the 372 families no miscarriages or stillbirths took place. Expressing this in another way, the 318 accidents took place in 53 per cent of the families while in 47 per cent no accidents occurred. Solomon gives an even lower percentage (36.5 per cent) of families in which accidents occurred. So while one finds that syphilis is an important factor in increasing fetal death, we must recognize that the action is selective. The two

TABLE I

					FAMS.	PREGNANCIES
Number of families with	1	pregnancy			63	63
" " " " 2	"	"			72	145
" " " " 3	"	"			70	210
" " " " 4	"	"			42	168
" " " " 5	"	"			36	180
" " " " 6	"	"			29	174
" " " " 7	"	"			18	126
" " " " 8	"	"			15	120
" " " " 9	"	"			11	99
" " " " 10	"	"			9	90
" " " " 11	"	"			1	11
" " " " 12	"	"			3	36
" " " " 13	"	"			2	26
" " " " 15	"	"			1	15
					372	1463
Showing number of pregnancies per family.						

TABLE II

					FAMS.	BIRTHS
Number of families with	1	living birth			125	125
" " " " 2	"	"			85	170
" " " " 3	"	"			70	210
" " " " 4	"	"			44	176
" " " " 5	"	"			28	140
" " " " 6	"	"			20	120
" " " " 7	"	"			8	56
" " " " 8	"	"			6	48
" " " " 9	"	"			1	54
" " " " 10	"	"			1	10
" " " " 11	"	"			1	11
" " " " 12	"	"			1	12
" " " " 13	"	"			1	13
					396	1145
Showing number of living births per family.						

accompanying tables show the number of pregnancies by families and the number of living births by families.

As in only 63 was there a single pregnancy (in this case also a living birth) and as in 175 families no accidents were recorded, in 112 or 30 per cent of our families two or more living births had taken place. A matter of further interest is the number of pregnancies and births per family. As the table shows, the number of pregnancies averaged almost exactly 4 (3.9 plus) per family and the children born alive averaged a little less than three in the 373 families regarding whom exact information was obtained. The 318 accidents to pregnancy were divided as follows: Miscarriages 222, stillbirths 96. In both cases it was the first pregnancy that gave the highest number—66 ending in miscarriages and 25 in stillbirths. The second pregnancy ended in a miscarriage 45 times and in a stillbirth 14 times.

*Syphilis and the Living Child.*—In the 1,463 pregnancies there were 318 fetal deaths, leaving 1,145 living children.

Number living births .....	1,145
“ children dead .....	233
“ living children .....	912
“ children with syphilis in study .....	443
“ children with plus W.R. but not examined ....	43
“ children examined without syphilis .....	54
“ children not examined .....	372

Very little can be said of the 233 deaths among children in the families of our syphilitic children. Practically none were attributed by the parents to syphilis, which is in accord with the well known fact that inherited syphilis is rarely recorded as a cause of death. How much of the “premature infant” marasmus, pneumonia, infectious diseases, and the like which were recorded as the cause of death were primarily due to syphilis or the result of a secondary condition grafted upon a syphilitic child with lowered power of resistance is purely a matter of conjecture. We can only point to the fact that the mortality rate of over 200 per thousand is much higher than the rate for children of the same age and social condition in St. Louis. Leaving the deaths aside our study shows that almost one-half (443 to be exact or 48.5 per cent) of the 912 children living at the time these 396 syphilitic families came under our observation, were infected with syphilis as shown by clinical exam-

inations and confirmed by the Wassermann test. We were surprised to find the large total of children not examined as it had been our feeling that we had been fairly successful in obtaining examination of the entire family. There were 54 brothers and sisters examined who had negative Wassermann reactions and 43 who had positive Wassermann reactions, but who were not studied clinically or brought under treatment for one reason or another. Many of these "not examined" members were beyond the age limit for the pediatric clinic and others were in the families of children coming from a distance.

#### SYPHILIS IN PARENTS AND CHILD

In only 80 out of the 396 families could a definite history of syphilis in either or both parents be obtained. Although a special effort has been made to examine, serologically at least, the parents of the syphilitic children, we were able to obtain examinations in but 188 of the 396 or a little less than one-half. The parents of some of the children were dead or missing, but in many instances the father or mother balked at anything more than the treatment of the child.

The results of the Wassermann tests were as follows:

Father only, 13 families.

W.R. 4 plus—1

W.R. 3 "—2

W.R. 2 "—3

Negative — 7 (no treatment in 3—after treatment in 4).

Mother only, 151 families.

W.R. 4 plus—64

W.R. 3 "—31

W.R. 2 "—32

W.R. 1 "—3

Negative — 21 (no treatment in 15—after treatment in 6).

Father and Mother—25 families.

Father—positive 18—negative 7 (after treatment—2).

Mother " 22—" 3

In one instance the husband was 4-plus positive and the wife negative. In another instance both were Wassermann negative, although the father admitted having had syphilis and the child was clinically positive with a 4-plus reaction.

It is not wise to lay too much stress upon these data regarding the parental infection as no conclusion of value can be drawn except that 90 per cent of the 176 mothers examined gave definite evidence

of syphilis. This in no way means that in the other 10 per cent the mother was not syphilitic at the time the child was born, as many of the parental infections dated back years—some over twenty years before the patient bringing the family into our study was born. There is no question but that the time element enters into the question of a plus or minus Wassermann reaction and the longer the distance from infection the less likely is the mother to give a conclusive serologic test. In three mothers of our series positive Wassermann reactions became negative several years later *without* treatment. An attempt was made to give treatment to the syphilitic mothers and in a number of instances the children of subsequent pregnancies were negative for syphilis both clinically and serologically.

## CLINICAL DATA

In this section data regarding the signs and symptoms are tabulated with a view to indicating their relative frequency and time of occurrence. One hundred ninety-seven of the 443 cases belong to the so-called "infantile" group and 246 to the "late" group.

## CLINICAL FINDINGS IN INFANTILE SYPHILIS

Table III shows the order of frequency of the more important signs observed.

TABLE III

	CHIEF COMPLAINT CONFIRMED ON EXAMINATION.	FOUND ON EXAMINATION, NOT NOTED BY PARENTS.	TOTAL	PER CENT
Eruption	62	32	94	48
Spleen enlarged	0	93	93	47
Rhinitis	56	25	81	41
Epitrochlear enlargement	0	28	66	33
General adenopathy	0	38		
Liver enlarged	0	64	64	32
Clinical signs neurosyphilis	15	15	30	15
Rhagades	8	14	22	11
Osteochondritis with pseudoparalysis	18	0	18	9
For W.R. only	10	0	10	5
Condylomata	0	6	6	3

Whether more than one of the signs occurred in the same patient is not indicated. Such an arrangement would practically necessitate a consideration of each case individually.

*Eruption.*—The total number of infants with a history of cutaneous eruption would be 109 (55 per cent) if the mothers' account of the symptoms were to be accepted as authentic. It was considered wiser, however, to include only those cases whose rash was observed and known to be of syphilitic origin. Of the 94 cases with syphilitic eruptions 78 were classified as macular; 9 as maculopapular; and the rest papular or vesicular. Seven of the macular eruptions were described as "circinate." A total of 59 cases (63 per cent) were described as having the eruption on the palms and soles. The records are not explicit on whether or not this was the only distribution of the rash in these cases. We feel safe in saying, however, that in the majority of instances where rash appeared on the palms or soles it was also found elsewhere on the body.

In 58 cases, the age at onset of the eruption was definitely stated. In 12 cases the eruption appeared at birth or during the first week of life. In 45 cases (80 per cent of those whose age at onset was recorded) the eruption appeared before the sixth week of life. In practically all cases the eruption had disappeared by the time the patient was three months old.

As is well known, rhagades, or the radiating scars found at the mucocutaneous junctions around the mouth or anus, are the result of intense local eruptive manifestations. Of the 22 infants in this series reported as having rhagades, anal rhagades were recorded in only 4 cases, and in these the mouth was also involved. "Mucous patches in the mouth" were noted in three cases with rhagades. One patient was brought to the clinic at the age of two for excision of a deforming scar at the left angle of the mouth. In another case, the cheeks were joined to the gums by dense fibrous scar tissue.

*Rhinitis.*—The figure for this symptom would total 95, or 48 per cent of the infantile cases, if 14 unauthenticated histories were included. In many cases it is difficult to rule out the "ordinary cold," but the greater profuseness of discharge, the greater chronicity, and the rapid response to antisypilitic therapy are important diagnostic features. "Bloody snuffles" were recorded in 7 of the 81 cases (9 per cent). "Saddle nose," a depression of the nasal bridge following some cases of rhinitis, was noted in 5 cases (6 per cent). In these cases rachitic deformity with prominence of the forehead resulting in what might be called "pseudo-saddle-nose" was ruled out.

The age of onset was recorded in 75 cases. In 30 (40 per cent)

rhinitis was present at birth. In practically all the other cases, the symptoms appeared between the second and seventh weeks of life, the second and third weeks being next to the first in frequency. In the five cases with "saddle-nose," the nasal stoppage was naturally more persistent, the deformity being so marked in two of them that even antisyphilitic treatment brought no relief. Except for these, the rhinitis had disappeared by the end of the third month in practically all cases.

*Enlargement of the Spleen.*—It is interesting that this sign was found with practically the same frequency as the eruption. As a possible manifestation of hereditary syphilis it is of greater significance when present in infants under four months old. Later on the condition may accompany such common disturbances as rickets, the exudative diathesis, etc., though of course in such cases a suspicious history calls for a Wassermann test.

*Enlargement of the Liver.*—In practically all cases with hepatic enlargement, splenic enlargement was also present. The latter, however, was often present without the former.

*Lymphadenopathy.*—As shown in Table III the frequency of this condition in infantile lues makes it an important though certainly not a pathognomonic sign of the disease. Epitrochlear lymphadenopathy, which was found without general lymphatic enlargement in 28 cases, is a sign of considerable importance in babies under two years, especially during the earlier months. Although tuberculosis and rickets may also cause epitrochlear enlargement, the frequency with which the sign is encountered in infantile syphilis should keep the physician on his guard.

*Osteochondritis (or epiphysitis).*—This occurred in 9 per cent of our infantile cases. In 14 of the 18 cases described one or both arms were involved. One case was diagnosed during the first week of life. The commonest age at onset was four weeks. We encountered no case with epiphysitis after the end of the fourth month of life. "Pseudoparalysis," due to tenderness on motion, was present in all cases. In addition to the cases listed, four had a typical history of osteochondritis with pseudoparalysis in early infancy, but as they were brought in after the symptoms and signs had disappeared they are not included in the table.

*Neurosyphilis.*—Of the thirty cases with clinical signs of neurosyphilis 5 were hydrocephalic, 5 were mentally deficient, 10 had con-

vulsions, and in the remaining 10 spasticity of one or more extremities was found. Results of spinal fluid Wassermann tests will be given elsewhere.

Cases listed "For Wassermann reaction only" were included if the result was positive. In all ten there was no clinical evidence of heredosyphilis. These cases, together with many others which proved to be negative, were tested in the majority of instances because of the discovery of syphilis in some other member of the family.

It is of interest that thirty cases found to be syphilitic were brought for entirely unrelated diseases. Twenty of the syphilitic cases had rickets.

Symptoms and signs less frequently encountered are enumerated in Table IV.

TABLE IV

	NO. CASES
Onychia	5
Edema of legs	4
Jaundice	3
Dactylitis (multiple)	3
Parrot's nodes	3*
Retina "peppery"	3
Strabismus	3
Osteoperiostitis	2
Keratitis (gonorrheal?)	2
Ophthalmia neonatorum	2
Blindness (cause?)	2
Synechiae (gonorrheal)	2
Edema of face	2
Anasarca	2
Alopecia	2
Ulcers of soft palate	2
Gonorrheal vaginitis	2
Spina bifida	1
Nystagmus	1
Ulcers of groin	1
Cretinism	1

\*Rickets not excluded.

#### CLINICAL FINDINGS IN LATE HEREDITARY SYPHILIS

The total number of cases of "late" hereditary syphilis (i.e., patients over two years of age and with manifestations not peculiar to the infantile type) was 246. In 51 of these a definite history of infantile syphilis was obtained; in 76 such a history was specifically



denied; in 119 it could not be determined whether or not the child had had the infantile form of the disease.

In Table V the more important "late" symptoms are arranged in the order of their frequency in our series.

TABLE V

	CHIEF COMPLAINT CONFIRMED ON EXAMINATION.	FOUND ON EXAMINATION.		
		NOT NOTED BY PARENTS.	TOTAL	PER CENT
Interstitial keratitis	57	12	69	28.0
Mental retardation	35	3	38	15.4
Polyadenitis	2	27	29	11.8
Hutchinson's teeth	0	22	22	9.0
Enlarged liver	0	18	18	7.3
Enlarged spleen	0	17	17	6.9
Unequal pupils	2	13	15	6.1
Rhagades	0	14	14	6.0
Periostitis (tibia)	6	7	13	5.3
Arthritis (knees)	12	1	13	5.3
Pegged teeth	0	11	11	4.5
Convulsions	11	0	11	4.5
Fixed pupils	0	11	11	4.5
Saddle nose	0	10	10	4.0
Complete blindness	9	0	9	3.7
Chorioretinitis	0	8	8	3.3

*Keratitis.*—As the table shows, this was by far the commonest "late" manifestation encountered in the series. It occurred in the right eye alone in 11 cases; in the left eye alone in 7 cases; in both eyes in 51 cases. It occurred in white males in 23 cases; in white females in 32 cases; in colored males in 5 cases; and in colored females in 9 cases. This proportion of 28 males to 41 females bears

TABLE VI

AGE AT ONSET	NO CASES
4 yrs.	4
5 "	6
6 "	8
7 "	13
8 "	11
9 "	8
10 "	4
11 "	5
12 "	4
13 "	3
14 "	3

out the observations of other authors that females are much more susceptible to heredosyphilitic interstitial keratitis than are males.

As this symptom is so striking the age at onset was accurately given for each case.

The age of seven years is thus seen to be the commonest age at onset, and also the average age at onset for this series.

*Mental Retardation.*—Fifteen and four-tenths per cent indicates a decidedly high incidence of this condition. Where possible all cases were referred to the neurologists for examination, but a number of the parents were so indifferent and uncooperative that the careful observation necessary to an accurate estimation of the mental status of the children was out of the question. All grades of mental deficiency were encountered from idiocy to the higher types described as "backward in school," "difficult to get along with," "mental age several years behind chronological." The milder degrees of deficiency were far more common. Two cases of juvenile tabes were not included in this group. Paretic colloidal gold curves were obtained in two cases diagnosed as juvenile general paresis.

*Dental Disturbances.*—Teeth were not considered "Hutchinsonian" unless they (upper central incisors) were found to be typically wedge-shaped with semilunar notches. There is a deplorable tendency to call any irregular or notched incisors "Hutchinson's," especially if the Wassermann reaction be positive. The frequency of dental malformations other than "Hutchinson's teeth" should be emphasized. Particularly common are "pegged teeth," i.e., wedge-shaped, tapering central upper incisors, without notching. They were present in 4.5 per cent of our cases. Changes in the other teeth,—"pinched off" enamel, malformed molars, narrow "fish-teeth," missing lateral incisors, are receiving more and more attention in the literature. All were encountered in our series, though infrequently.

We found "Hutchinson's triad," interstitial keratitis, nerve-deafness, and "Hutchinson's teeth" existing in the same patient in only two cases.

*Enlargement of the Liver.*—One of the cases with this condition deserves special mention. A colored boy of nine had had interstitial keratitis at the age of five. Scars of this were present at the age of nine when his liver began to enlarge. At no time could the parents be induced to have him treated properly. When last seen his liver

filled the entire upper abdomen, and large rough nodules could be distinctly felt. The spleen also was considerably enlarged. There was no ascites. He had lost a great deal of weight, and at the time of examination was quite emaciated. Both treatment and further observation were refused.

*Involvement of the Central Nervous System.*—Of the 443 cases examined, 79 (17.8 per cent) presented clinical manifestations of involvement of the central nervous system. Twenty-one were infantile (i.e., 10.8 per cent of the infantile cases) and 58 were late cases (23.6 per cent of the late cases). In 206 cases the spinal fluid was examined. The spinal fluid Wassermann proved to be positive in 63 cases (30.6 per cent of those tested). Of the 75 infantile cases tested, 24 (32 per cent) were positive. Of the 130 late cases tested 39 (30 per cent) were positive.

Table VII shows the relation between the results of the spinal fluid Wassermann tests and the clinical manifestations.

TABLE VII

SPINAL FLUID W.R. CLINICAL SIGNS	POSITIVE		NEGATIVE		NOT TESTED	
	YES	NO	YES	NO	YES	NO
Infantile cases	10	14	2	49	9	113
Late cases	28	11	8	83	22	93
Total	38	25	10	132	31	206

From Table VII it will be seen that definite agreement between the spinal fluid Wassermann reaction and the clinical neurological findings was noted in 170 of the 206 cases whose spinal fluids were tested. Definite disagreement was noted in 35 cases. As might be expected, the majority of the discrepancies (25 cases or 71 per cent) were serologically positive and clinically negative; and of these 25 cases the proportion of infantile cases was both relatively and actually greater.

Among the less common neurological manifestations not listed in Table V were those shown in Table VIII.

Some of the cases with neurologic manifestations were of sufficient interest to warrant special mention. W. H., white male, was first seen at the age of twenty-six. When twelve years old his vision began to fail, and he found that he could not walk steadily. There was no noticeable change in his vision during the six or seven years prior to his admission to the clinic. Little of importance could be

TABLE VIII

	NO. CASES.
<i>Known optic atrophy—total</i>	10
Complete, right eye	1
Complete, left eye	0
Partial, bilateral	3
Complete, bilateral	6
<i>Hemiplegia</i>	9
With pos. spinal fluid	4
Chorea	4
Nerve deafness	4
Diplegia	4
Nystagmus	2
Juvenile tabes	2
Juvenile paresis	2
Epilepsy	1
Internal hydrocephalus	1

learned of his family history. On examination he was found to be oriented, and showed good attention and cooperation. There was bilateral optic atrophy with light perception only. The right pupil was larger than the left, both were fixed, and both were irregular. Motion of any of the eye muscles was impossible, there being practically complete ophthalmoplegia. The gait was that of spinal ataxia, with a broad base, due partly to his very poor vision. The cremasteric and deep tendon reflexes were absent. There was no loss of temperature sense. The senses of pain and touch were lost over the whole trunk and legs, except the upper half of each thigh up to the level of the iliac crests. The Wassermann reaction of both blood and spinal fluid was four plus in the cholesterin antigen only. The spinal fluid cell count was 33. The Pandy test for globulin was two plus. The colloidal gold test was 0132100000. The case was obviously one of juvenile tabes with a remarkable degree of ocular and sensory involvement. Re-examination two years later showed that his condition had not changed in any respect. The disease was so advanced that treatment was not considered advisable. He had never had treatment previously.

J. F., female, white, age eight years, had "always" been subject to attacks of headache and vomiting at irregular intervals. At the age of three she suddenly lost the use of both legs and of both arms and hands. Two days later she became unable to speak. Within three months she was "apparently normal." She had a second attack one year afterward and a third two years still later from

which she suffered at the time of her admission to the clinic. At the time of her last attack she became completely bald. When seen in 1916 her mentality was markedly impaired, there were general choreiform movements, spasticity of both legs. Dr. Schwab noted that though there was unquestionably an organic lesion of the pyramidal system, the finding of a normal spinal fluid might indicate that the central nervous condition and the heredosyphilis were independent. The blood Wassermann was 4 plus on two occasions. On reexamination five years later (she had had three injections of salvarsan and very little mercury) her condition was the same, except that there were marked contractures of the arms and legs. Chorio-retinitis (bilateral) was also present. This case is cited as an example of severe central nervous disorder in a heredosyphilitic, with two previous attacks and partial recovery, and with a negative spinal fluid where a pathological fluid was to be expected. It should be noted that the mother of this patient had a negative Wassermann reaction, and an "old luetic perforation of the soft palate."

*Cases with Less Common Manifestations.*—Table IX gives the rarer signs of "late" heredosyphilis, not included in the foregoing tables.

TABLE IX

	NO. CASES.
Ulcer of pharynx	5
Anal condylomata	5
Alopecia	4
Gumma of bone	4
Gangrene of extremities	2*
Vulval condylomata	2
Placques on tongue	1
Ozena	1
Perforation of nasal septum	1
Nose occluded	1

\*Both cases with gangrene of the extremities were in children with hemiplegia. In one it was necessary to amputate the leg just above the knee. In the other the distal phalanges of the second and fifth toes of the foot on the paralyzed side had sloughed off spontaneously.

Of the cases of gummata of bone, one, a girl of twelve, had had a deep ulcer of the lower right leg for two years, due to an underlying gumma of the tibia, and another ulcer of the frontal region, due to a gumma of the skull, for one year. There were scars of what had no doubt been gummata on the left shoulder, right elbow, and right groin. Her liver was markedly enlarged, her spleen less so.

Her right lower eyelid was absent on account of scar formation. The effect of treatment upon this case will be considered in the third article.

*Miscellaneous.*—It is worthy of note that 39, or 16 per cent, of the late cases were brought for the Wassermann test only, i.e., because of the discovery of syphilis in some other member of the family. Thirty-five, or 14 per cent, were brought for entirely unrelated diseases.

# A STUDY OF 443 CASES OF HEREDITARY SYPHILIS WITH ESPECIAL REFERENCE TO RESULTS OF TREATMENT

## PART II. END RESULTS OF TREATMENT

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(Received for publication, June 6, 1922)

WE HAVE experienced considerable difficulty in classifying our cases from the standpoint of therapy, both as regards treatment received and results obtained. As a result of factors not under our control and explained in the previous section, there has been a wide variation in the amount and continuity of treatment. Furthermore, our own ideas have changed considerably regarding the character and amount of treatment required in hereditary syphilis since the work was started some twelve years ago. At first, for example, we used considerable neosalvarsan intramuscularly, which later was given up because of the pain produced by injections. This we found increased the difficulty in getting parents to bring their children back to the hospital or clinic for further treatment. As the work progressed a system was gradually evolved in the clinic which was described in detail by Dr. Jeans in January, 1921, and which had been in use since about 1917. Essentially this consists of a course of three intravenous injections of arsphenamine at weekly intervals every two months, followed by weekly injections of a 1 per cent bichloride of mercury solution. In addition grey powder is given by mouth at home two or three times daily in a dosage of from  $\frac{1}{2}$  grain to 1 grain according to the age of the infant or child. In infants an attempt is made to keep up this routine treatment for one year and in older children for two years. If at the end of this period the Wassermann reaction is negative, treatment is discontinued for several months, and the routine is started again whenever the Wassermann reaction becomes positive. Many of the central nervous cases in addition have been treated intraspinally by

the Swift-Ellis method. Cases with open or frank symptoms have been treated more intensively at first until the active symptoms were brought under control. We have found in going over our cases that despite the use of every possible means to carry out this routine treatment large numbers of our cases have discontinued treatment for one reason or another, and consequently the amount of treatment that the individual cases in our series have received varies quite widely.

As it is impossible to discuss the amount of treatment received in each individual case in such a large series, we have finally decided for the purpose of our paper to divide our cases from the standpoint of therapy into four groups, taking into consideration the amount, character, and duration of the therapy. These four groups are designated "satisfactorily," "fairly satisfactorily," "incompletely," and "unsatisfactorily" treated. Infants and children who were treated routinely over a period of time as outlined above or in the earlier years over an equivalent period have been recorded as "satisfactorily treated." Cases treated over a long period, but not reporting with sufficient regularity to receive an equivalent amount of antisyphilitic treatment or cases treated with a satisfactory amount of drug but with too short duration have been grouped as either "fairly satisfactorily" or "incompletely treated." All cases treated for less than three months were considered "unsatisfactorily treated," although in many instances during this period they received a large amount of arsphenamine and mercury and marked clinical improvement followed. In the same way cases treated longer than three months, but reporting too infrequently, or whose home treatment was too indifferently carried out, have been grouped with the "unsatisfactorily treated" cases.

In classifying the results of treatment we have divided our cases into "cured," "improved," "unimproved," or "recovered," and have necessarily made rather arbitrary qualifications for each case. Patients have been regarded as cured only when the Wassermann reaction has become repeatedly negative as a result of treatment and all clinical evidence of syphilis has completely disappeared. We have encountered a number of cases which have become clinically and serologically negative either without treatment or with an unsatisfactory amount of treatment. As we are studying in this paper the results of treatment we have classified these under a sep-



arate group as "recovered," as the apparent cure which has taken place in these cases seemingly has borne no relation to the therapy. In the group of "improved" we have included: first, patients whose clinical signs have improved but whose serological findings have not improved; secondly, those whose Wassermann reactions have become less strongly positive and whose clinical signs have improved or at least not increased; and third, patients whose blood Wassermann has become negative but whose spinal fluid Wassermann has remained positive. In the group of "unimproved" we have included those cases where there has been no improvement in the serologic findings or clinical picture, or where they have become worse despite the therapy in individual cases. As stated in a previous paragraph it has been exceedingly difficult to group these cases in an entirely satisfactory manner, yet we feel that classification is essential as the only other method is to give in detail the history of each one of the four hundred-odd cases.

#### INFANTILE CASES

Before discussing the prognosis and results of treatment of the "Infantile" cases, it is necessary to consider some of the factors which are related to the morbidity and mortality of syphilis in infants. While syphilis in older children is only rarely the cause of death, it plays a very distinct rôle in the production of infant mortality. This rôle, however, is definitely influenced by such considerations as race, age, nutrition, etc.

Of our 197 cases less than two years of age, 137 lived and 60 died—a mortality for the group of 30.4 per cent, or 304 per thousand. This figure may be compared with the Infant Mortality rate for St. Louis which averaged about 90 during the period of our study. For our entire series of 443 cases the mortality was 17.6 per cent, which may be compared with Müller and Singer's<sup>2</sup> percentage of 35.0 for a similar series.

*Race.*—One hundred thirty-one of our infants were white. Of these 48 (36.6 per cent of the total) died. Sixty-six were colored (33.5 per cent of the total). Of these 12 (18.1 per cent) died. Thus, though the incidence of hereditary syphilis among the colored children of this community is from seven to eight times as high as among the whites and though 33.5 per cent of our infantile cases

were colored, the mortality rate for our colored syphilitic infants was distinctly lower than that for the whites. This we attribute largely to the greater prevalence of breast feeding among the colored race.

*Number of Pregnancy.*—Though there is ample evidence in our experience, as in that of others, that the oldest children, i.e., those nearest the parental infection, are more likely to be syphilitic, the mortality among children of first pregnancies was no higher,—in fact it was lower, than that among children of second and third pregnancies.

*Age.*—Of the 60 infantile cases known to have died, 42, or 70 per cent, died before the age of six months. As in the nonsyphilitic babies the mortality among premature infants was very high. Fourteen of our cases were recorded as premature, and of these six died (43 per cent). Three of the five infants known to have been born two months before term died.

*Feeding.*—Our data confirm the opinion that, as in other diseases, the character of the infant's diet is a factor of the utmost importance in determining the outcome of a case of infantile hereditary syphilis. For many social reasons, among them neglect, poverty, ignorance, and illegitimacy, infants with hereditary syphilis are not likely to receive proper artificial feeding when this becomes necessary. One hundred thirteen of our syphilitic infants were breast fed at the time of examination, or, in the case of older infants, for at least the first six months. Twenty-eight of this group died (25 per cent). Of 16 infants on "mixed feeding," 4 died (25 per cent). Of 32 infants on condensed milk 20 died (62.5 per cent). Of the 36 infants on other or unknown diet 8 died (22.2 per cent). The enormous mortality among the babies fed on condensed milk is most striking. In one of the earlier papers from the clinic it was shown that the syphilitic babies averaged three pounds less than the average weight for babies of the same age.

*Causes of Death.*—For our 60 cases with fatal outcome, the assigned causes of death were as shown in Table I.

Necessarily the infants with syphilis who died at a very early age cannot be classified as satisfactorily treated according to our standards.

*Treatment.*—One of the 60 fatal cases received thorough treatment, according to our classification, but died in the third year of

TABLE I

Hereditary syphilis alone	15
“ “ with bronchopneumonia	4
“ “ “ marasmus	3
“ “ “ nephritis	1
“ “ “ pertussis	1
“ “ “ convulsions	3
Gastroenteritis	4
Bronchopneumonia with gastroenteritis	5
“ alone	8
“ with pyelitis	1
“ with mediastinal abscess	1
Lobar pneumonia	1
Streptococcus septicemia	2
Reaction to salvarsan	2
Measles	1
Erysipelas	1
Hydrocephalus	1
“ and tuberculosis	1
Malnutrition and tuberculosis	1
Diphtheria	1
Osteomyelitis, cellulitis, nephritis	1
Influenza	1
Unknown	1

life. Three were treated “fairly satisfactorily,” four “incompletely,” and fifty-two “unsatisfactorily.” The one thoroughly treated case was one of twins; always drowsy, very deficient mentally, and subject to frequent convulsions. The spinal fluid Wassermann was positive at first, but became negative after three years’ treatment. First signs of infantile syphilis appeared before the eighth week in 63.5 per cent of the surviving cases, and in 70 per cent of the fatal cases. Observation and treatment were begun before the eighth week in 51.8 per cent of the surviving cases, and in 58.3 per cent of the fatal cases. These figures are cited to show that there was no important difference between the surviving and fatal cases so far as the time of appearance of signs and the age at the time of first observation are concerned. It is true that the majority (70 per cent) of the fatal cases died before the age of six months. But in view of the fact that only 16 patients (26.6 per cent) died before the age of eight weeks, there was sufficient time between first examination and death for the majority of the others to have received intensive treatment if they had been brought regularly. Lack of cooperation on the part of the parents prevented not only proper treatment but also frequent observation of the patients. It

must, of course, be borne in mind that "treatment" means not only the administration of antisyphilitic drugs, but constant dietetic supervision in the clinic by the physician and in the home by the social workers. Neglected, deserted children are given care without which antisyphilitic treatment alone could accomplish little or nothing. All these things considered, the significant facts remain that 86.6 per cent of the fatal cases were practically untreated, as against 58.4 per cent of the surviving cases; and that only one thoroughly treated case died.

The treatment of hereditary syphilis is painful, expensive, difficult, distressing to parent, child, and physician. If, as regards amelioration of symptoms, future well-being of the patient, and rate of mortality, the treated cases cannot be shown to do better than the untreated, then we must consider carefully the value of the measures we have taken during the past years. Concerning the effect of treatment on mortality our figures indicate that antisyphilitic treatment is of great importance in saving the lives of syphilitic infants; though its importance is at least equaled by that of the child's state of nutrition.

TABLE II  
SHOWING THE EFFECT OF EARLY AND THOROUGH TREATMENT IN INFANTILE SYPHILIS

TREATMENT BEGUN AT LESS THAN 2 MONTHS OLDS (FOLLOWED MORE THAN 3 MONTHS)					
	CURED	IMPROVED	UNIMPROVED	RECOVERED	?
Satisfactory	7	1	3*	0	1
Fairly Satisfactory	3	0	1	0	2
Incomplete	0	3	3	1	4
Unsatisfactory	0	4	3	2	2

\*One of these had four-plus spinal fluid Wassermann.

Of this total of forty cases 31 were adequately followed and the end-results definitely ascertained. There were 10 cures (32.2 per cent) under treatment, and only 4 unimproved (13 per cent). Of the entire group of 137 surviving infantile cases, end-results were definitely ascertained in 77. (See Table III.) Nineteen of the 77 were cured (24.6 per cent) under treatment, and 7 unimproved (9 per cent). Thus distinctly better results were obtained in cases whose treatment was begun at less than two months of age.

Table III gives the results of treatment for the 77 surviving infantile cases.

TABLE III

SHOWING END RESULTS AS RELATED TO TREATMENT IN 77 CASES OF INFANTILE SYPHILIS

	CURED	IMPROVED	UNIMPROVED	RECOVERED
Treatment Satisfactory	13	5	4	0
Fairly Satisfactory	5	2	3	1*
Incomplete	1	10	6	1
Unsatisfactory	0	18	4	0

\*Wassermann became negative too quickly to be due to treatment.

Table III brings up several important matters for consideration. Omitting the 60 cases whose end-results could not be learned, we find that of the 77 thoroughly followed cases 35 were "improved" (45.4 per cent). In only 7 of these cases could the improvement be attributed to long-continued routine treatment, leaving 28, or 36.3 per cent of the 77 cases, which seemingly improved without treatment or with such treatment as we do not consider today as sufficient. These were nearly all cases whose clinical signs either improved or disappeared, while the Wassermann reaction remained positive. Whether clinical signs disappear more quickly in treated cases than in untreated is a question on which we are unable to give accurate statistics. The reason for this is that the duration and intensity of the eruption, rhinitis, or other manifestations of infantile syphilis vary greatly in individual cases, whether treated or untreated. Moreover, accurate data on the duration of manifestations which seldom last more than a few weeks could not be obtained unless the infants were kept under daily observation while symptoms were present. This is impossible when the majority of the infants are treated in the dispensary.

As noted above, most of the improved cases became free from symptoms, but continued serologically positive. Table IV shows the effect of treatment upon the Wassermann reaction in the 61 "infantile" cases on whom we have accurate follow-up statistics.

TABLE IV

SHOWING EFFECT OF TREATMENT ON WASSERMANN REACTION

	W.R. POSITIVE TO NEGATIVE.	W.R. POSITIVE TO WEAKER POSITIVE	NO EFFECT ON W.R.
Treated satisfactorily	18	5	9
Treated incompletely or unsatisfactorily	9	4	16

From this table it will be seen that the serologic results were about twice as good in the well-treated cases as in the inadequately treated cases. The number of cases becoming spontaneously negative or less strongly positive is, however, decidedly large. Further, the table shows that 30 per cent of the satisfactorily treated cases underwent no change in the positivity of the Wassermann reaction.

Returning for further consideration of Table III we find 7 well-treated patients unimproved (serologically and symptomatically) as against 10 inadequately treated patients. Six patients became serologically and clinically negative with inadequate treatment. In 18 cases, serologic and clinical cure may be attributed to treatment. Naturally the great majority of the cases in which the results of treatment could not be determined were among the unsatisfactorily treated group.

Table V is instructive in that it shows the relation between spinal fluid Wassermann and central nervous symptoms and signs, and also the relation between both of these and the results obtained by treatment. Cases whose end-results could not be ascertained were not included.

As indicated in Table V, nearly all the cases in which good results

TABLE V

SP. FL. W.R.		POSITIVE		NEGATIVE		NOT TESTED		TOTAL
CLINICAL LESIONS		YES	NO	YES	NO	YES	NO	
Cured	Treatment							
	Satisfact.	1	1		11			
	Fairly satisf.				4		1	19
Recovered	Incomplete	1						
	Unsatisfact.							
							1	6
Improved	Satisfact.						1	
	Fairly satisf.						1	
	Incomplete	1*					3	
	Unsatisfact.		2		3			
					2			
Unimproved	Satisfact.		1		6		3	35
	Fairly satisf.		2		2		14	
	Incomplete	2		1	1			
	Unsatisfact.	1	1		3	1	1	17
			1				4	

\*Blood and spinal fluid Wassermann became rapidly negative

N.B. The discrepancy between the figures of this table, and those of Table VII of the article giving social and clinical data, lies in the fact mentioned above, that cases whose end-results could not be ascertained were omitted from this table.

were accomplished by treatment were cases without laboratory or clinical evidence of syphilis of the central nervous system. As might be expected, cases with only laboratory evidence of neurosyphilis did better than those with clinical evidence. Similar statistics of "late" cases are given below.

What is the fate of children surviving "infantile" hereditary syphilis? what proportion of patients who have had "infantile" hereditary syphilis develop "late" manifestations? what is the effect of treatment upon the development of these late symptoms? these are important and interesting questions. So far as we know not one of our infantile cases has developed late manifestations. Inasmuch as our patients were seen between the years 1912-20, sufficient time has not as yet elapsed for our cases to have passed completely through the period when "late" manifestations may develop; for, as noted in the first section, some of these cases developed "late" manifestations at the age of ten years or more. As we have not seen our early cases develop "late" manifestations, we cannot of course express an opinion as to the importance of treatment in infantile cases in preventing their development.

We found, however, that 51 of the patients admitted to the "late" syphilis group gave histories which indicated quite definitely that there had been lesions of active syphilis in infancy. These were "untreated" cases. This figure (20.7 per cent) indicated only the frequency of previous infantile syphilis for this group.

From the foregoing considerations it is clear that a very large number of infants not succumbing early to the disease may be expected to become clinically negative whether treated thoroughly or not. Both clinical and serologic negativity are obtained about half as frequently in the untreated or slightly treated as in the well-treated cases. As far as our observations in our own cases go, there seems to be little tendency for the infantile cases which have been treated, to develop manifestations of syphilis later.

#### RESULTS OF TREATMENT IN "LATE" CASES

Only 18 of the 246 cases with "late" hereditary syphilis died, a mortality of 7.3 per cent. Our experience thus coincided with that of others, in that the mortality among our "late" cases was no higher than that for a similar group of nonsyphilitic children. With

regard to the effect of treatment on the mortality of this group, it is safe to say that there was no relation between them, except that one patient died as the result of a severe reaction to arsphenamine. The one fatal case having had satisfactory treatment was a child with cerebrospinal syphilis who contracted diphtheria and died in convulsions. Thus with older children must be regarded only as a contributory cause of death.

The criteria given for infantile syphilis as regards cure, recovery, improvement, and lack of improvement,—also whether treatment was satisfactory, fairly satisfactory, incomplete or unsatisfactory,—have been followed in our study of the late cases.

The commonest sign of late hereditary syphilis—interstitial keratitis—is one on which the effects of treatment can be observed with some degree of accuracy. Table VI gives results of treatment in 32 completely followed cases with interstitial keratitis.

TABLE VI\*

TREATED SATISFACTORILY OR FAIRLY SATISFACTORILY			TREATED INCOMPLETELY OR UNSATISFACTORILY		
Complete recov.	Impr.	Unimpr.	Complete recov.	Impr.	Unimpr.
14	4	0	4	8	2

It would appear from these figures that though a considerable number of cases of interstitial keratitis may improve without treatment, complete clinical recovery takes place three and half times as frequently in the adequately treated cases. We agree with Morton Smith<sup>13</sup> and others who affirm that arsphenamine is of distinct benefit rather than harm in cases of syphilitic interstitial keratitis, although we have seen children with latent syphilis (plus W.R. without clinical signs) develop acute keratitis as a result of intensive arsphenamine injections.

One patient, a girl of ten, had had epiphysitis at the age of three months; she received no antisyphilitic treatment until she was admitted to the clinic at the age of ten, with bilateral interstitial keratitis. She was treated regularly for six months with considerable improvement. Then, the clinical signs having subsided, she followed the common and natural tendency and remained away from the clinic. Three months later she returned with an exacerbation

\*Results given in this table are only the clinical effects on the local condition.



of her keratitis of about two weeks' duration. She reported somewhat irregularly for fifteen months and was then lost track of. When in the course of this investigation the patient's aunt was treated she refused to reveal the child's address, claiming, with disregard for the truth, that the doctors had broken off five needles in the child's arm and made her eyes worse. Inasmuch as this exacerbation of keratitis occurred after two and a half months without treatment, antisyphilitic drugs could not properly be blamed for it.

One colored girl was admitted in 1914 at the age of twelve because of tonsillitis which had been discovered by the school doctor. Because "pegged teeth" were found on examination, a Wassermann test was made and proved to be positive. Neither the pegged teeth nor the tonsillitis sufficed to stimulate the mother to permit antisyphilitic therapy. When seen seven years later, at the age of nineteen, she had been blind for about a year and a half, as the result of an extremely severe interstitial keratitis. Permission for a second Wassermann test was refused. Incidentally, the patient had married a few weeks before this final examination. As in all our cases of proved hereditary syphilis, the future offspring of this girl will be carefully watched with a view to throwing some light on the still debated subject of syphilis of the second and third generation.

Judging from our cases the severity of the keratitis at onset has no definite relation with the duration of corneal opacity. One girl whose keratitis began at the age of twelve and who also had hard, palpable liver and spleen, ulceration of the tongue and one tonsil, and absence of the uvula, had only a slight haziness of the right cornea at the time of onset. When seen again five years later the condition of the right cornea was practically unchanged. On the other hand, we have seen cases with keratitis so severe at onset as to cause blindness, clear up without treatment in a surprisingly short time. It should be repeated, however, that such an occurrence is far more common in treated than in untreated cases.

Among the most satisfactory cases from the therapeutic point of view were two with multiple gummata of the bones, and also those with syphilitic periostitis.

Among the least satisfactory cases from the therapeutic point of view were, as might be expected, those with involvement of the central nervous system. There seems to be no justification for con-

sidering hereditary neurosyphilis as, properly speaking, a "late" manifestation. Indeed, there is no conclusive evidence to show that spirochetal infection of the central nervous system does not occur early (i.e., in utero) as Fordyce<sup>14</sup> and others have claimed for the acquired disease.

It is true that juvenile tabes usually has its onset, symptomatically at least, at about the age of adolescence. Our two cases were not exceptions to this rule. It is not unreasonable to assume, however, that if these patients had been subjected to spinal fluid examination during infancy, evidence of neurosyphilis would have been found. Many of our cases were classified as "late" simply because of their age at the time of first examination. A number were followed from infancy to later childhood; a large number gave histories which indicated neuropathology during the first year or two of life.

One girl with right-sided hemiplegia was first seen at the age of five. Her mother said she had been "born paralyzed and was always queer." At the time of her first examination the ends were missing from the second and fifth toes of the right foot; the distal end of the right great toe was red, "due undoubtedly to a gangrenous process." A note made at that time stated that "from her actions it seems likely that there is some mental impairment." Her eye-grounds had a "peppered appearance, and retinitis characteristic of syphilis." (Dr. Green.) Her mental deficiency was not considered marked. She received practically no antisypilitic treatment and it is doubtful whether it would have benefited her. Five years after her first examination a tenotomy was performed to relieve a contracture of the right tendo Achilles. The Wassermann reaction on the spinal fluid was reported "plus-minus." Her blood Wassermann changed in five years from four plus to negative, without treatment. She was seen again eight years after her first examination, at the age of thirteen. Her mental age was then considered to be five years behind her chronologic age. She was subject to brief convulsions. On one occasion she "chased the whole family with a butcher-knife." Her blood Wassermann, repeated at this time, was negative. Unfortunately her spinal fluid Wassermann could not be repeated at this time. This case is a particularly interesting example of practically complete serologic recovery, with irreparable organic damage to the central nervous system.

Another similar case, seen first at the age of five and again at the

age of thirteen, with spastic paralysis of all four extremities, choreiform movements, marked mental deficiency, and positive Wassermann in both blood and spinal fluid, became Wassermann negative in both blood and spinal fluid at the end of eight years without treatment. The clinical condition remained unchanged.

These cases are interesting contrasts with the case of D.B., a colored boy seen at the age of six months. He had been subject to convulsions since the age of three months. The physical examination was negative except for an enlarged spleen. His blood and spinal fluid Wassermann reactions were four-plus. During the next three years he received fourteen injections of salvarsan, 41 injections of mercury. He was supposed to have taken one-fifth grain of gray powder three times a day. Owing to financial conditions and to occasional lapses into non-cooperation, the treatment was at times given at irregular intervals,—one interval being of nearly a year's duration. The treatment was considered "fairly satisfactory." He received no intraspinal treatments. At the end of three years there was no change in the number or severity of his convulsions, though his physical examination was negative. The Wassermann reaction of both his blood and spinal fluid remained four-plus.

One girl of five, with marked involvement of the entire central nervous system, was treated "incompletely" over a period of three years. During her three courses of treatment in the hospital, however, she was given intensive treatment and in addition received six intraspinal injections of mercury albuminate. At the end of this three year period, her spinal fluid and blood Wassermann remained four-plus and her clinical condition was unchanged.

These case-reports and the statistics given in the table below indicate the futility of treatment in cases of hereditary neurosyphilis with marked clinical manifestations. As Jeans has intimated,<sup>4</sup> patients with positive spinal fluid Wassermann are very difficult to render Wassermann-negative by treatment. Such cases, however, should receive prolonged and intensive treatment in the hope of preventing their regression from "laboratory" to "clinical" cases.

The two cases in Table IX, with positive spinal fluid and with clinical signs of neurosyphilis, recorded as "cured" under thorough treatment, were both cases without mental disturbance, whose spasticity cleared up and never returned, whose blood and spinal fluid Wassermann tests remained negative.

In Table VII will be found the general results of treatment in the 228 living "late" cases, omitting 56 cases followed for less than three months, and omitting the 19 cases whose end-results could not be determined.

TABLE VII

	CURED	IMPROVED	UNIMPROVED	RECOVERED
Treatment				
Satisfactory	10	17	3	0
Fairly satisfactory	11	22	3	0
Incomplete	2	7	7	2
Unsatisfactory	0	27	25	17

It should be repeated that under "improved" are grouped cases showing all varieties of clinical and serologic improvement; and that under "recovered" are grouped all cases becoming clinically and serologically negative with inadequate or no treatment.

For this group of 153 "late" cases we find 73 "improved" (47.7 per cent) a trifle higher than the percentage improved among the infantile cases. Improvement could be attributed to treatment in 39, or 25.5 per cent, of the 153 cases,—a considerably higher percentage than that for the infantile cases. However, in 34, or 22.2 per cent, of the 153 cases, improvement could *not* be attributed to treatment. It will be remembered that for the "improved" group of infantile cases, the proportion of well-treated to inadequately treated cases was far lower.

In the "unimproved" group of "late" cases, we find 6 well-treated patients as against 32 inadequately treated.

Of the infantile cases 6 patients became serologically and clinically negative with inadequate treatment, as against 18, or three times as many well-treated cases; a great balance in favor of the latter. Contrast now the corresponding figures for the "late" cases. No less than 19, or 12.4 per cent, recovered completely with inadequate treatment as against 23, or 15 per cent, with adequate treatment. (The two cases "cured" on "incomplete" treatment were so recorded because of the long period of time over which treatment was distributed). In short, for the whole group of "late" cases, there are about five times as many "unimproved" among the inadequately treated cases. Otherwise there is very little essential difference between the well-treated and the inadequately treated cases.

What are the effects of treatment for this group from the serologic point of view? The answer to this question is contained in Table VIII.

TABLE VIII

	W. R. POS. TO NEGATIVE	W. R. POS. TO WEAKER POS.	NO EFFECT ON W. R.
Treated satisfactorily or fairly so	22	35	6
Treated incompletely or unsatisfactorily	23	15	13

It must be emphasized for the purpose of evaluating the statistics of Table VIII that only 114 cases were completely followed (i.e., retested) serologically. This leaves 39 cases not accounted for, all of them in the "unsatisfactorily treated" group. In any event, the number of inadequately treated cases becoming Wassermann-negative is strikingly high, more than equaling that of the well-treated cases. The fact that adequate treatment has rendered the Wassermann less strongly positive in more than twice as many cases as has inadequate treatment; and that it has had "no effect on the Wassermann" in less than half as many cases, may perhaps properly be considered to save the day for therapy in "late" hereditary syphilis. It is perfectly clear, however, that the treatment of "late"

TABLE IX

SP. FL. W.R.		POSITIVE		NEGATIVE		NOT TESTED		TOTAL
CLINICAL		YES	NO	YES	NO	YES	NO	
Cured	Treatment							
	Satisfact.	2	1		7			
	Fairly satisf.				10		1	23
	Incomplete				1		1	
Recovered	Unsatisfact.							
	Satisfact.							
	Fairly satisf.							19
	Incomplete			1	1			
Improved	Unsatisfact.				3		14	
	Satisfact.	2	3		8	1	3	
	Fairly satisf.		2		17		3	73
	Incomplete			1	4		2	
Unimproved	Unsatisfact.		1		9	2	15	
	Satisfact.	1	1		1			
	Fairly satisf.			1	2			37
	Incomplete	4		2		1		
	Unsatisfact.	9			3	6	6	

hereditary syphilis is far more disappointing than is that of infantile syphilis, and that in this condition, time will effect many recoveries, both clinical and serologic.

In Table IX which corresponds with Table V for the infantile cases, is shown the effect of the presence or absence of cerebrospinal syphilis on the curability of "late" hereditary syphilis.

This table requires no additional comment.

Table X, which, like the others, omits the cases whose end-results were not determined, combines the results of treatment in both the infantile and "late" cases.

TABLE X

	CURED	IMPROVED	UNIMPROVED	RECOVERED
Treatment				
Satisfactory	23	22	7	0
Fairly satisfactory	16	24	6	1
Incomplete	3	17	13	3
Unsatisfactory	0	45	29	21

## REACTIONS TO TREATMENT

It would be both unprofitable and inaccurate to enumerate the thousands of injections which our patients have received, together with the number of reactions encountered. At first an attempt was made to do this; but the figures obtained gave an altogether inadequate idea of the number of reactions, particularly to mercury. We have, therefore, confined ourselves to the following statements, for whose accuracy we can vouch.

## REACTIONS IN INFANTILE CASES

*Mercury.*—Some years ago, when treatment by inunction was employed, the only undesirable effect noted was an abdominal dermatitis in one case. This method of treatment was abandoned simply for the reason that the mothers could not be relied upon to give the inunctions properly.

With regard to the daily doses of gray powder, in use at the present time, diarrhea is so commonly encountered that mothers are warned to reduce the dose as soon as the bowels become loose. Many of our infants are at first unable to take even small doses of gray powder on this account; but later, as they become accustomed to it, tolerate the drug very well. Salivation, unless it is extremely

profuse, is of course an unreliable indication of reaction to mercury during infancy. We have not warned mothers against it, as they would then discontinue the drug for the slightest "slobbering" on the part of the baby. We have never seen a case of stomatitis in our syphilitic infants, which we have felt to be attributable to mercury. Dental disturbances are much more likely to be due to the disease than to the treatment.

In a large majority of cases,—practically all, in fact, intramuscular injections of one per cent solution of bichloride of mercury have been followed by a moderate degree of induration. As a rule this induration is painful for only a few hours. In only two cases have abscesses developed, and these were due to the fact that the injections were not given deeply enough. Frequent urinalyses have not led us to agree with some observers that proteinuria is a common result of bichloride injections.<sup>15</sup> In the very few cases where it has occurred the injections have been temporarily discontinued.

*Arsenicals.*—As stated by Jeans,<sup>1</sup> intramuscular (deep) injections of neoarsphenamine were tried a number of years ago. In a short time, four cases developed very severe, painful indurations, lasting for many months. One case resulted in a deep slough. Practically all mothers requested intravenous injections for the children, after the intramuscular route had been tried. Our results are thus not in agreement with those of Fordyce and Rosen.<sup>16</sup>

Nearly all the treatments in our clinic have been given by internes under the supervision of Dr. Jeans. Even allowing for "breaking in" new men, the number of painful indurations following accidental extravasation of arsphenamine during intravenous injections, has been extremely small. This may be due to the fact that the number of "failures to give arsphenamine" intravenously is distinctly large. If difficulty in entering a vein is encountered, such as the needle passing through both walls, with extravasation of blood, etc., the attempt to inject the arsenical into that particular vein is at once abandoned.

The commonest reactions to the arsenicals are nausea and vomiting, usually within an hour or two following the injection,—nausea, of course, being complained of only by the older children. We have felt, as have others, that, granted a reliable preparation, one of the commonest causes of such reactions has been too rapid injection of the solution,—a temptation difficult to resist in a busy clinic, espe-

cially in the treatment of children, whose every struggle may mean "losing" the vein once "found." Too much shaking of the solution, and fear of over-alkalinization have also contributed to the number of reactions. Cyanosis with vomiting was noted in only two cases. The only infant who went into collapse following an injection was one with cerebrospinal involvement who received his salvarsan very early in the course of treatment. Two infants died (at home) one three days, and one two days following injections of salvarsan.

One of these was the case mentioned by Jeans<sup>1</sup> as the cause of our abandoning the administration of salvarsan by way of the longitudinal sinus. A third case died two days after receiving a dose of salvarsan. The day before death, however, the child was found by the family physician to be suffering from bronchopneumonia. Had this been present on the day of treatment, the injection would not have been given, for it is a rule never to treat cases with marked acute or chronic disease, or with fever, unless it can be shown that such disease is due directly to the syphilitic process.

#### REACTIONS IN "LATE" CASES

Except that salivation may be given more weight in older children, there are no further remarks to make on reactions to mercury. Marked "accidental indurations" following intravenous arsenotherapy occurred in a larger number of late than infantile cases, due possibly to the greater difficulty in restraining the older children during the injection. In a number of the "late" cases, cough and flushing of the face occurred within a half hour of the injection. Such attacks were relieved very quickly by the intramuscular injection of adrenalin, which is always kept ready in the treatment room.

#### REACTIONS TO INTRASPINAL TREATMENT

In all, 48 intraspinal injections were given, 5 of which were of mercurialized serum and 43 of which were of salvarsanized serum. Fever, occasionally as high as 103° or 104° F., occurred after 21 injections. Eleven of these patients complained also of nausea and vomiting, 4 of nausea alone. Ten of the injections were followed by no reactions at all. Convulsions occurred twice. Nearly all the patients suffered from headache, but how many headaches were



due to lumbar puncture alone and how many to the treatment is of course not known. All intraspinal therapy was carried out in the hospital.

#### SUMMARY AND CONCLUSION

This study was undertaken with the purpose in view of determining whether or not the end-results of the intensive work with hereditary syphilis during the period 1912-1920 were of such a nature that future work along the same line is indicated or justified. During this period 443 patients with the disease were observed and followed with adequate hospital, clinic, and social service facilities available at all times. It is impossible to state the exact cost but when the time and salaries of physicians and social workers, equipment, drugs, etc., are considered we are justified in estimating it at many thousands of dollars.

From the social standpoint we have found the group as a whole unsatisfactory and difficult to deal with. Lack of interest on the part of parents has led a large part of our material to discontinue treatment long before dismissal by the physician. While here and there families have been encountered who have cooperated most satisfactorily, their number is far overshadowed by the group of uncooperative. Thus, out of 230 living patients in whom end-results are known, only 52 followed out a thorough course of treatment; while 95 were absolutely uncooperative. A middle group of 83 cases continued treatment with a fair degree of regularity for a time, but dropped away before discharged. Allowing for the 78 deaths in the group there are still left 125 patients who for one reason or another were lost track of and a large per cent must be included with the group of "uncooperative." In our experience, in spite of thorough and intensive follow-up work, only a third of the hereditary syphilitic patients were given the benefit of a satisfactory or fairly satisfactory course of treatment, and we question whether this figure can be improved under ordinary conditions.

In discussing the results of medical treatment two viewpoints must be considered: first, the results of treatment in the individual case of hereditary syphilis; and secondly the results of treatment for the group of 443 cases as a whole. So far as the individual case is concerned our results show that a given case has a fair chance of clinical and serological recovery or improvement; that

such recovery or improvement may seemingly take place on little or practically no treatment, but that the chances for cure or improvement are very much better for a case thoroughly treated with arsenicals and mercury than for one poorly treated. The earlier the treatment is started the better the result. If the given case has either serological or clinical evidence of involvement of the central nervous system, the chances for recovery or improvement are poor. One is justified, therefore, in treating a case of hereditary syphilis thoroughly with the expectation that it will be benefited.

As regards the group as a whole the results have been disappointing. The infant mortality rate is three times the rate for infants from all diseases. This is despite treatment and is seemingly dependent upon the extent to which the infant's nutrition and metabolic function have been impaired. Further, approximately one-third of the cases have had involvement of the central nervous system and as a group these have shown little improvement. Although active lesions in these cases have been checked, the residue of the infection leaves a child who as a rule belongs to the socially unfit. Considering the group of 308 cases whose end-results are known we find them briefly as follows: Cured or recovered 67 or 22 per cent; improved 108 or 35 per cent; unimproved 55 or 17 per cent; died 78 or 25 per cent. Thus we find that in our entire group, regardless of the amount of treatment received, 43 per cent were either unimproved or died. Despite the intensive work during this period only 22 per cent of our cases are known to have been cured or recovered.

Certainly this cannot be considered a brilliant showing. While one is justified in urging thorough treatment in the individual case, our group results clearly show that from a social or group standpoint the treatment of hereditary syphilis in the infant or child leaves much to be desired. The problem is best attacked by reaching the syphilitic woman or mother before and during pregnancy. This is all the more apparent when one takes into consideration the fetal mortality. While by no means advocating the neglect of the syphilitic child, we feel that the results to be obtained are so poor as a whole that our efforts should be directed much more to the prenatal clinic than to the pediatric clinic, and that the only satisfactory solution

of the problem of hereditary syphilis is its prevention rather than its cure.\*

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\*We wish to express our indebtedness to the many members of the Pediatric staff who have been interested and carried on the routine clinical and laboratory work during the period of years the cases reported in our series were followed; and particularly to Dr. P. C. Jeans who has had the direction of the syphilitic clinic and work during a large part of this time.

## EXTRAGENITAL CHANCRE

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(Received for publication, January 29, 1922)

THE incidence of extragenital chancre, according to Dr. Highman, in the most recent work on dermatology, is estimated at 10 per cent. When it is remembered that about 10 per cent of males and 40 per cent of the females infected with syphilis have negative histories, it is not unreasonable to presume that the percentage is even greater. That these lesions may resolve with or without treatment is an important factor in explaining why many of them are not diagnosed; and the fact that "the whole medical profession" today seems to be treating syphilis does not tend to promote early diagnosis. The physician not specializing in this disease is not apt to consider the probability of extragenital chancre until he is reminded of it.

Aside from the fact that the first case herein reported is considered one of autoinfection of the penis and that the second shows an unusually rapid resolution of the initial lesion under daily intravenous injections of arsphenamine in a case where infection was due to carelessness in personal protection, this short paper will contain little of especial interest to men trained in this line of work. However, even specialists are prone sometimes to overlook initial lesions of syphilis in unusual situations, and I feel we cannot be too often reminded of the possibility of their occurrence. It is for these reasons that I am presenting the following two case histories:

CASE 1.—T. M., aged twenty-five, white, male, admitted to the Louisville City Hospital, April 28th, 1920. He contracted gonorrhea two months ago and had been discharged by his physician. His last exposure was about one month before the lesion appeared. The patient first noticed a small, slightly ulcerated sore on his upper lip, April 2, 1920. This gradually enlarged and on April 20, eighteen days after appearance of the lesion on his lip, a sore appeared on the corona glandis. On April 28, the patient was sent to Dr. I. N. Bloom's Clinic at the Louisville City Hospital, where he was examined by me. The sore on the upper lip, as will be noted by the photograph, presented a convex appearance



Fig. 1.—Initial lesion before treatment.  
(Case 1.)



Fig. 2.—Appearance after five weeks' treatment.  
(Case 1.)



Fig. 3.—Autoinfection before treatment.  
(Case 1.)



Fig. 4.—Appearance after five weeks' treatment.  
(Case 1.)



Fig. 5.—Initial lesion before treatment.  
(Case 2.)



Fig. 6.—Appearance one week later after treatment.  
(Case 2.)



with an indurated base, the lip being swollen to twice its original size in the central portion and tapering gradually toward the corners of the mouth. The surface of the lip was smooth and exuded a serous material. Other than a feeling of fullness there was no pain. The sore on the corona glandis was ulcerated, slightly concave and macerated. The base was indurated and painless and had a characteristic button-like feel. There was a general adenopathy, including the anterior and posterior cervical and both epitrochlear glands. Over the body and face was a maculopapular eruption. Smears were made from the penile and labial lesions and the patient sent to the arsphenamine room, blood for a Wassermann being taken before the drug was administered. The dark-field apparatus was out of order, or, at any rate, it was impossible to get a proper focus, and *Spirochetæ pallida* were not found. On the following day I attempted to demonstrate the germ from the penile sore and serum from one of the inguinal glands, but was unsuccessful. In view of the fact that a full dose of arsphenamine had been given, failure was to be expected. The patient was given arsphenamine twice a week until nine doses had been administered. The second photographs were taken five weeks after the first.

The chief point of interest in this case is the suggestion (which to my mind is an established fact), of an autoinoculation from the upper lip to the corona glandis. The inference is that infective material was carried by the fingers from the lip to the penis in directing the act of urination. The weak link in the chain is my failure to demonstrate the spirochetæ. However, I hope in a large measure this has been overcome by the history and the photographs taken before and after treatment, also the fact that a ++++ Wassermann was found before treatment. The second picture shows the resolution of the lesions which was uniform, during the course of the treatment.

CASE 2.—The history in the second case is of professional interest as a reminder to correct the careless handling of known syphilitics of which we are sometimes guilty. On February 25, 1921, C. S., a physician, was called to administer an anesthetic to a patient who had a secondary eruption on his body. There were no mucous patches or sores about the mouth, and the physician neglected to wear gloves. Three days before (February 22) the index finger of the right hand of the doctor had been cut with a piece of broken glass. His hands were well washed in water and alcohol after giving the anesthetic. On March 21, 1921, a small pimple appeared in the region of the original wound on the index finger. This gradually became larger. A Wassermann test was made two weeks later which was negative. On April 7 the physician came to me for examination. There was no glandular enlargement or eruption present. The sore on the finger presented a circumscribed, convex appearance, indurated, ulcerated in the center and covered with a glazed film. The lesion was of doughy consistency and presented a typical picture of Hunterian chancre. *Spirochetæ* were found in the lesion.

April 7, 1921 the patient received 0.6 gm. arsphenamine, and 0.5 gm. were given on the eighth, ninth, eleventh, twelfth and thirteenth. Wassermanns made on April 11, and April 14 were negative.

A urinalysis was made each day during treatment, and except for a high specific gravity, was negative.

April 15, 1921. The patient presented an eruption on the arms, legs and a few scattered lesions on the body. He gave a history of having eaten fresh strawberries the night before. He complained of a moderate amount of itching. The lesions on the forearms and legs had the appearance of the annular type of erythema multiforme, having edematous bases with depressed whitish centers, and disappearing on pressure. On the chest the lesions were composed of pin-point papules, erythematous in appearance. This eruption gradually faded within three days without treatment other than the administration of laxatives. The second photograph, taken April 15, 1921, showed only a slightly wrinkled skin over site of the chancre with no induration.

The Wassermann test having continued negative, and believing I had to deal with a toxemia, whether intestinal in origin or due to arsphenamine being uncertain, I discontinued the arsphenamine although it had been my intention originally to give three more injections, and then began the use of mercury salicylate intramuscularly.

The two series of pictures show plainly how rapidly the lesions disappeared under the daily administration of arsphenamine.



## THE DIAGNOSIS OF EARLY SYPHILIS\*

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(Received for publication, April 22, 1922)

DURING the past six months we have been digesting the results of a survey of 231 cases of early syphilis in the records of the Section on Dermatology and Syphilology since its organization in 1916. In the strict sense of the term these are early active cases, since in 210 either a chancre or a secondary eruption or both were found at the time of examination; the condition could not, therefore, be construed as latent. Of the twenty-one cases included as recurrences, all presented active lesions and in only two was the duration of the infection longer than two years. The overwhelming proportion of the series was seen within the first six months of the disease. In this and subsequent papers we shall compare our observations with one or another series of observations, recorded by other writers, but especially with that of Fordyce which includes 243 secondary cases, 60 per cent of which were of one year's duration or more. By such comparisons we shall also be able to point out certain of the presumptive effects of treatment on early syphilis. Of our own series not more than 10 per cent of the patients had had what would now be regarded as the beginning of effective treatment for the disease, that is, six arsphenamine injections with some form of mercurialization. Even if local treatment of the chancre is included the total number of patients subjected to any form of treatment does not exceed 25 per cent.

We shall avoid the reiteration of familiar statistical details of the percentage of genital and extragenital lesions, the incubation periods, the morphology of the lesions with respect to induration, scar,

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and so forth, and shall proceed to point out the significant facts with reference to the early diagnosis of syphilis.

No one step in syphilologic progress is more important than the popularization of the dark-field examination of the lesions of early syphilis. To this much to be desired end the studies of Fildes and Dudding and the statistical material from recent army experience so effectively presented by Moore have been important contributions. It will be recalled that Fildes and Dudding criticized the British Navy for a ratio of 1 patient with syphilis diagnosed in the primary stage to 4 in whom the condition was recognized only after the appearance of secondaries. Up to that time our army ratio had only been reduced by modern diagnostic methods as far as 1 to 4.5. These authors pointed out that it is easily possible to identify 65 per cent of genital sores as chancres on first examination with the dark-field by the finding of the *Spirochete pallida*; this percentage nets a ratio better than 1 to 1. Only 14 per cent of those in whom the condition was not thus identified subsequently were shown to be syphilitic by the use of the Wassermann follow-up. Moore confirmed the latter figure in a series of 800 genital lesions seen in the Paris hospital of the American Expeditionary Forces. He found 54 per cent of chancres among the genital lesions examined by dark-field. His comment on the comparison between the finding of 46 per cent chaneroids in this hospital under the direction of experts, and diagnoses aggregating 75 per cent chaneroids in patients seen by the average line medical officer supports the principle that inexperienced observation of the genital lesion, without the use of the dark-field, results in a 30 per cent margin of error in the diagnosis of primary syphilis. Much of this error is, we believe, the product of the survival of antiquated morphologic notions of the appearance of the chancre as an aid to diagnosis, and the persistence of the habit of teaching medical students the untrustworthy differential criteria of prespirochetel days. If the medical student will learn that there is no way to identify a genital lesion except by the dark-field, and the Wassermann test, he will be a much safer servant of the public than with his present equipment of half truths about induration, erosion, multiplicity, painlessness, and so forth.

In eighty early cases of our series, the patients had consulted physicians before they came to the Clinic. Seventy per cent had received correct diagnoses, leaving a margin of error of 30 per cent

identical with that reported by Moore. This showing, though good, is far from ideal. The analysis of the margin of error is, however, not a perfectly fair index of professional inadequacy, since the progress of a case is very apt to yield some evidence that helped us, but was not available to the physician who first saw the patient. The analysis is none the less interesting. Ninety-four per cent of the patients seen by physicians had received some treatment, so that it is fair to assume that in 24 per cent of the cases, treatment had been begun without giving the patient a diagnosis. This argues an obvious laxity, both with respect to the status of the patient as a carrier of infection and to the question of whether or not he had early syphilis. No doubt the physicians who treated these patients had decided that the patients had chancroids and not syphilis, they were planning to wait for secondaries, or to take a subsequent Wassermann test. The error and the risks for patient and public are none the less plain (Table I).

TABLE I

DIAGNOSTIC ERRORS IN EIGHTY CASES OF PRIMARY AND SECONDARY SYPHILIS

	CASES
Chancroid	10
Gonorrhea	3
Carcinoma or tumor	3
Furuncle	2
Eczema	2
Vincent's angina	1
Tuberculous tonsil and glands	1
Herpes simplex	1
Coryza	1
Smallpox	1

Most of the patients were questioned as to whether they had previously had dark-field examinations. Only three of eighty could recall anything resembling our procedure. One was from the army, one from the navy, and one had been examined by a general practitioner. The third patient, after dark-field diagnosis and one arsphenamine injection, deserted his evidently conscientious and competent physician and only came to us because of a complete relapse. We could secure no data on the number who had had Wassermann tests, but we recall with vividness one patient who before coming to the Clinic had been used as a donor for transfusion during his secondary

incubation period, ten days before the florid outbreak and, therefore, at the presumptive height of his spirochetemia.

It cannot be too strongly impressed on physicians that the clinical diagnosis of chancre has been replaced by laboratory methods, and that those who do not or cannot apply the dark-field and the Wassermann test systematically should not deal with it at all. Moreover, the day should not be far distant when a diagnosis of chancroid, made within four months after the onset of a genital lesion, shall be generally recognized as naïve.

The dark-field examination of the primary lesions seen by us yield 66 per cent of positives. In interpreting this and all other results of dark-field examination of suspected lesions, it is proper to take into consideration the age of the lesion when the first examination was made, and the treatment given the patient prior to examination. Figure 1 illustrates the reciprocal relation in our series between the effectiveness of the dark-field and of the Wassermann reaction on the blood during the first six months of the disease. Many physicians are prone to invoke the Wassermann test when they lack equipment for the dark-field examination, without realizing that the dark-field is at its best when the Wassermann is at its worst in early syphilis, and vice versa. The finding of positive Wassermann reactions by the second week in 70 per cent of our cases indicates that the Wassermann prop is at best not a bad one, and deserves more extended use. In connection with the dark-field examination of small suspected early lesions, we have found the subcutaneous injection of saline followed by aspiration as suggested by Schultz a very useful procedure when surface examination of the lesion is unsuccessful.

With respect to the effect of the treatment on the chancre, modern teaching urges that no treatment be applied until the dark-field examination has been repeatedly made and found negative. There can be no doubt of the value of this principle, and it should be vigorously preached. Our series of patients, however, showed that treatment, local or general, does not necessarily make the dark-field useless. Of seventeen chancres in treated patients, eleven yielded positive dark-fields. Of the eleven patients with positive dark-fields, eight had had local treatment including cautery and three had been treated systematically with arsphenamine and mercury. The conditions of these three patients are of interest because they

belong to the class of monorecidives. Two had each received one arsphenamine injection, and the third while in the army, had had three arsphenamine injections and three injections of mercury salicylate. His chancre had healed, then recurred and was followed by secondaries. In one case of recurrent chancre, *Spirocheta pallida* were very few in number in the lesion, but in the inguinal lymph nodes they were extraordinarily numerous and active.

If eleven positive dark-fields can be obtained in seventeen locally treated chancres, it is evident that repeated examination after salt solution soakings even in treated lesions, is well worth while. In the meanwhile, however, the Wassermann reaction may clear up the diagnosis. Nothing could better evidence the transitory effect of a dose or two of arsphenamine on an infectious lesion than the course of the relapsing chancres described.

Of 122 cases with primary lesions, 71 per cent had a palpable satellite bubo. This lacks a good deal of the invariable incidence so much emphasized by Ricord and his pupils and is in a way another index of the break-down of old-time clinical criteria in early diagnosis.

Glandular aspiration of the bubo is regarded as an effective method of finding the organism when the chancre yields a negative smear because of treatment or age. Twelve gland aspirations performed on the satellite bubo in our series yielded 50 per cent positive results. These were done by the older "dry" method. We believe that the recently suggested injection of saline and reaspiration is a valuable addition to the technic.

Our study of this series of patients prompts us still further to stress the efficiency of the dark-field in the recognition of secondary lesions, both in association with the general eruption and in subsequent less widely distributed recurrences. Of twenty-four dark-field examinations taken on mucous patches and condylomas, twenty-three yielded positive results. Due precaution was taken to eliminate by thorough scraping the *Spirochete refringens* and other saprophytic contamination, and to have the microscopic field viewed by an examiner accustomed to differentiating the *Spirochete pallida* from adventitious mouth spirochetes. Here again treatment in eight cases did not prevent our obtaining a positive dark-field, and the dark-field was negative in only two treated cases. This very high proportion should encourage the wide application of the

method when expert advice is available in interpreting the results.

Our Wassermann results on secondary syphilis are of some interest. Few observers rate the percentage of positive Wassermann reactions obtainable in untreated secondary syphilis below 95 per cent, and observers such as Boas, Craig, and Kolmer place it nearer 100 per cent. In a series of 221 patients, both treated and untreated, they obtained 96.1 per cent positives, and Vedder in a similar series of 310 patients obtained 91.0 per cent positives. The results in 160 cases of florid secondary syphilis are shown in Table II.

TABLE II  
POSITIVE WASSERMANN TESTS IN FRANK SECONDARY SYPHILIS

All cases as they come, treated and untreated.....	92.0 per cent
Some treatment, but not enough to cause complete involution of secondary lesions .....	95.7 per cent
Untreated cases .....	98.5 per cent

HISTORY OF CHANCERE  
PER CENT

	CHANCERE	NO CHANCERE	GENITAL	EXTRAGENITAL
Men	82	18	83	17
Women	58	42	64	36

There is a noticeable tendency in the literature to give the Wassermann test less than its just measure of confidence in florid secondary syphilis. Writers on the test take pains to guard themselves by allowing for the small percentage of untreated acute secondary cases with negative Wassermann reactions, by needlessly cautious statements, and by endorsing the diagnosis of an untreated secondary eruption over the head of a negative Wassermann reaction, if its appearance seems to support the opinion. Such a point of view deprives the test of a well-deserved confidence. We have in our records and can recall instances in which lichen planus and pityriasis rosea have been diagnosed syphilis by competent clinicians, because of a certain distrust, even of the repeatedly negative Wassermann reaction in the eruptive stage. We unhesitatingly believe that for the average physician the repeatedly negative Wassermann reaction in a case of untreated general eruption can be accepted as proof that it is not syphilis. The dilemma in deciding the status of an early eruption becomes acute only when, as a result of ineffective treatment, lesions recur but the Wassermann reaction remains negative.

We encountered a negative Wassermann reaction in the face of presumptive syphilis in seven cases; in five of these there was a definite history of treatment. The details of these cases and the method of reaching a diagnosis are indicated in Table III.

It is especially interesting to note the superiority of the dark-field over the Wassermann test in this group of cases as a means of detecting syphilis partially suppressed by treatment. The fact that spirochete-containing lesions may develop in patients who are actually under treatment and are Wassermann negative, has of course long been familiar in theory. The diagnostic worth of the dark-field procedure, however, is seldom more apparent than in this series where it proved decisive in five of seven Wassermann negative cases, and in the sixth was evidently applicable but the record contained no note of the result.

So serious at times is the difficulty of deciding, in the presence of a history of treatment, whether or not the condition presented by the patient is syphilis, that we believe in these days of the vanishing lesion, as Smith has so well called it, that each patient should have registered with a competent authority, such as the State Board of Health, under his notification number if not his name, the evidence on which his initial diagnosis was based. On his order this would then be accessible to physicians who might assume charge of his case after all gross evidence of the infection had for the time been obliterated.

One of the interesting and suggestive details of our study of early syphilis was the proportion of patients who although presenting obvious secondary lesions, had no evidence of a primary lesion at the time of examination and could give no history of one. Twenty-four per cent of the whole series, including men and women, with all types of lesions, gave no evidence in history or examination of ever having had a chancre. These data accord with our results in other surveys, in which we found that 25 per cent of men who are found to have syphilis in a general diagnostic clinic cannot give a history of a primary lesion. Data on the analysis of the proportion of men and women in this group may be found in Table II.

These percentages illustrate the difficulty of getting the woman under treatment in the primary stage. The masquerade of the chancre in men includes of course, the extragenital chancre, of which we saw a number, the intraurethral type, of which we saw no

TABLE III  
WASSERMANN NEGATIVE SECONDARY SYPHILIS (TREATED AND UNTREATED)

CASE	PREVIOUS TREATMENT	DARK-FIELD EXAMINATION	WASSERMANN REACTION ON THE BLOOD (SINGLE)	SPINAL FLUID	DIAGNOSIS BASED ON:
A347280	None	Negative	Negative	Negative	Chancre and macular eruption
A243265	Mercury pills	Positive	Negative	No data	History of chancre six months previous, papular eruption, condyloma, mucous patches, positive dark-field
A264581	Mercury pills, five months	No data	Negative	Wassermann reaction negative, Nonne negative, 12 cells	History of chancre six months previous, maculopapular eruption, mucous patches
A317015	Three arsphenamine injections	Positive	Negative	Negative	Chancre of lip, mucous patches, positive dark-field
A282497	Three arsphenamine injections	Positive	Negative	No data	History of chancre, pharyngitis, mucous patches, positive dark-field
A295467	Three arsphenamine injections, three injections mercury salicylate	Positive	Negative	Wassermann reaction negative, Nonne negative, 9 cells	Monorecidence (recurrent chancre); papular secondary syphilis of face, positive dark-field.
A212295	None	Positive	Negative	No data	History of chancre six months previous, no secondary eruption, mucous patches, positive dark-field



recognizable example, the chancre within the anal ring (invisible), one case, mild gonorrhea, and so forth.

In summarizing data on the cutaneous lesions presented in our secondary cases, we were surprised to note the high proportion of macular (roseolar) and maculopapular eruptions. We attribute this high percentage to two elements, the exceptional lighting of our examining rooms, and our ability to inspect patients during their twenty-four hours in the hospital after the first arsphenamine injection. The Herxheimer reaction thus observed, confirmed our initial diagnosis of faint and scarcely visible eruptions. Several of the patients had entirely escaped detection even by alert observers in less well lighted rooms. Undoubtedly under the conditions of average practice, and even in clinics where night work is done or daylight is poor, many of the fainter secondary efflorescences escape observation entirely. In patients treated by ambulatory methods, the physician usually misses the Herxheimer flare-up. We believe that wherever inspection is a factor in arousing a suspicion of syphilis or making a diagnosis, as in industrial and military medical work, much more attention should be given to the matter of illumination than has been the practice heretofore. The syphilographer belongs on the roof rather than in the basement of his clinic and his ability to cross-illuminate a faint macular eruption, especially in women, and to see it without the by effects of colored reflexes from walls and trees may at times be the crucial deciding factor between recognition and nonrecognition of an infection. (Table IV.)

All corymbose eruptions were recurrences. This predilection for corymbose configurations in generalized recurrences has been a striking feature of our experience.

Of 183 patients with frank secondary lesions, the incidence of a general adenopathy was much the same as of the primary satellite adenopathy, 69 per cent. We believe that it is quite possible that the foundation for the general adenitis is being laid at the same time that the bubo is appearing.

Of infectious lesions, the total incidence was 58 per cent. They were fairly evenly divided in incidence between the sexes, 75 per cent of the women and 64 per cent of the men having such lesions. It is probable that routine speculum examination of the women

TABLE IV  
TYPES OF CUTANEOUS SECONDARY SYPHILIS OBSERVED

	CASES
Macular	54
Maculopapular	28
Large macular	16
Grouped follicular	11
Papular	5
Corymbose papular	2
Psoriasiform papular	3
Grouped follicular and papular	2
Lichenoid miliary papular	1
Annular papular	1
Pigmentary follicular	1
Pigmentary papular	1
Papulopustular	1
Rupial	1

would have disclosed something more nearly approaching the high proportion of mucous lesions credited by Fournier to the female sex.

#### CONSTITUTIONAL SYMPTOMS

The impression that early syphilis is mainly a cutaneous disease is unfortunately too prevalent. On the other hand the systemic symptoms are remarkably inconspicuous for so serious an infection. Constitutional symptoms are estimated not to appear in more than 50 per cent of all secondary cases, and the so-called prorseolar symptoms, associated with the generalization of the infection before the appearance of the secondary eruption, seem distinctly uncommon. In our series of twenty-eight patients with chancres, from whom data on this point were collected, only four had prorseolar symptoms and these were of the mildest. The general distribution of constitutional symptoms in the series showed the tendency to female preponderance, mentioned by Fournier: Men 182, constitutional symptoms 78 (43 per cent); women 49, constitutional symptoms 31 (63.2 per cent).

The incidence of special symptoms is given in Table V.

The constitutional symptoms of early syphilis do not in general have high diagnostic value. Here and there a distinctive symptom stands out, but in general corroborative evidence must be sought from a thorough general examination and the Wassermann test before a diagnosis can be made. A review of the symptomatology assists in arousing suspicion rather than in making a diagnosis.

TABLE V  
SYMPTOMATOLOGY OF EARLY CONSTITUTIONAL SYPHILIS

	PER CENT		PER CENT
Sore throat	53	Iritis	3
Malaise	41	Vaginal discharge	3
Headache	24	"Anemia"	2
Loss of weight	18	Deafness	2
Fever	14	Hoarseness	2
Meningismus	8	Myositis and myalgia	2
Gastro-intestinal symptoms	7	Nocturnal ostealgia	2
Rheumatism	7	Periostitis	1
"Neurotic" symptoms	5	Arthritis	1
Bone disorders	5	Palsy of eighth cranial nerve	1
Pseudotuberculous symptoms	5	Insomnia (essential)	1
Nervousness	4		

The conspicuous place occupied by sore throat in early syphilis is at once apparent from Table V. Once physicians can be persuaded to give sore throats more than local examination, and strip such patients to the waist, the early diagnosis of syphilis will be advanced several points. Headache, if persistent, is an important symptom of secondary syphilis. If the occipital pain of meningismus be included as headache, the proportion of early syphilitic patients who have headache as a symptom rises to 31 per cent, or nearly one-third. On such evidence it is safe to surmise that in any practice, patients with a combination of persistent headache and sore throat, if adequately investigated for syphilis or if given a routine Wassermann test, and an inspection of the skin, would yield a harvest of early syphilitic infections.

Fever of a mild grade, seldom exceeding 100, afternoon temperature, is a fairly common accompaniment of the constitutional manifestations. The general clinician should be most on the lookout for confusion with tuberculosis and with typhoid fever. "Syphilitic typhoid," an intermittent fever with marked prostration and cachexia and a sparse roseola, is rare. On the other hand the combinations of slight fever, loss of weight, night sweats, gastro-intestinal symptoms, asthenia, nervous irritability and cough which early syphilis may present, especially in women, are important from the standpoint of differentiation from tuberculosis. The impossibility of diagnosing syphilitic pneumonitis by an intrinsic sign makes it difficult to determine just how often errors actually arise from the confusion of these two diseases in their early stages.

Cough is an unusual symptom in early syphilis, but pseudotuberculous pictures made up of other elements in our table are so far from unusual as to justify a Wassermann test in all cases of suspected early tuberculosis. Arthritic pains, anemia, and loss of weight, another group of symptoms by no means rare in both diseases, demand careful scrutiny. These symptoms are among the chief causes of error in the misdiagnosis of tuberculids as syphilis. The well recognized possibility that syphilitic infection superimposed on latent tuberculosis may cause a flare-up of the latter, must always be borne in mind.

Gastrointestinal symptoms in early syphilis range from anorexia to nausea and projectile vomiting associated with intracranial pressure in high grades of early cerebral and meningeal involvement and in precocious brain gumma. Nausea, vertigo, and vomiting with deafness and tinnitus also are expressions of changes in the eighth nerve, the nausea and vertigo expressing the labyrinthine and vestibular portions of the complex. Eusterman has called attention to the frequency of subacidity in cases of syphilitic catarrhal gastritis, but the symptoms of this condition are not highly specific.

The catch basket of "rheumatism," expressing the osseous, arthritic, and myalgic symptoms of early syphilis is responsible for errors of diagnosis. The systematic use of a sensitive Wassermann test in all aspects of bone, joint, and muscle involvement in patients between the ages of fifteen and thirty-five years would without question reap a harvest of early syphilis. Many of these symptoms of rheumatism have the vagueness expressed in the lay term "grippy." That they may constitute the prodromes or early manifestation of the generalization of the infection, makes their early recognition especially important. Traditionally the leading symptomatic feature of the bone symptoms of early syphilis is pain, nocturnal in character, exaggerated by heat and relieved by movement of the affected part. Overemphasis on these peculiarities would lead to the overlooking of a number of cases, since in not more than half of the patients with osseous changes under our observation has this syndrome appeared.

#### SUMMARY

A study of 231 cases of early syphilis, largely untreated, yields the following observations bearing on the diagnosis of early stages of the disease:

1. The diagnosis of early syphilis has become a laboratory problem, divided between the dark-field examination and the Wassermann reaction. Clinical criteria, while interesting, have lost most of their final diagnostic value. The primary stage especially, should no longer be overemphasized in teaching.

2. The dark-field examination showed 55 to 65 per cent of all genital lesions to be chancres outright.

3. In our consecutive series, irrespective of age, 66 per cent yielded positive dark-fields; 80 per cent were positive the first week, and none were positive after the ninth week.

4. Seventy per cent of the Wassermann tests made in the second week of the chancre were positive.

5. The dark-field detected *Spirochete pallida* in twenty-three of twenty-four moist secondary lesions, and in five of seven Wassermann negative, early, or recurrent secondary cases.

6. The dark-field on treated primary lesions is not hopeless. Eleven of seventeen cases yielded positives. Nonetheless the withholding of treatment until after repeated negative dark-field examinations needs to be vigorously preached.

7. Glandular aspiration of the satellite bubo of the chancre with dark-field examination of the serum yielded 50 per cent positives.

8. Of eighty patients who previously had seen physicians we found that only three had had dark-field examinations, one army man, one navy man, and one civilian.

9. The practitioner's margin of error in diagnosis was 30 per cent. In 24 per cent, treatment of some kind had been instituted while no diagnosis had been given the patient.

10. "Chancroid" is still the chief diagnostic pitfall. The attitude that every genital lesion is potentially a chancre until proved otherwise is the safest for public and patient. Diagnosis of chancroid should not be made until four months after the appearance of the lesion and following repeated negative Wassermann tests. "Cancer," "tumor," "herpes," "felon," are the masquerades of extragenital chancres.

11. One patient had been used as a transfusion donor before coming to the Clinic, while he had a chancre, and was at the height of his spirochetemia, and ten days before his secondary eruption appeared. The physician who used him as donor had evidently made no inquiry into his condition.

12. The Wassermann test in our secondary cases yielded the following: 92 per cent positive in treated and untreated, 95.7 per cent positive in those with slight treatment, 98.5 per cent positive in those without treatment.

13. We believe the repeated positive Wassermann test in secondary syphilis is a safer guide for the inexperienced than the characteristics of the eruption. If it is negative, the dark-field or the combination of findings may make the diagnosis.

14. In the aggregate, 24 per cent of patients with florid secondary syphilis, a high percentage, could give no history of chancre, even though their secondaries were fully developed. This included a physician with secondaries, but no sign of a primary lesion (needle prick?).

15. Women are especially apt to give no sign of a primary lesion (concealed, short duration, and so forth).

16. Macular eruptions preponderate in our secondary cases. This we believe is an effect of special attention to lighting on our part, and is of great importance where inspection is used as a clue to syphilis as in industrial and military hygiene.

17. More than half of our patients had infectious lesions when seen (68 per cent). More women than men had infectious lesions (75 per cent in contrast to 64 per cent), which makes them even more effective carriers than men. In this we are in accord with Fournier.

18. Half our patients had constitutional symptoms with secondary eruptions; much fewer in the preeruptive stage (four in twenty-eight).

19. Women show a markedly greater tendency to constitutional symptoms than men (63 per cent in contrast to 43 per cent). In this also we are in accord with Fournier.

20. The leading constitutional symptoms are sore throat (53 per cent), headache, and head pain (31 per cent).

21. Combinations of mild fever, sweats, loss of weight, asthenia, gastrointestinal symptoms, nervous irritability, arthritic and myalgic pains with anemia are frequent and are easily confused with early tuberculosis. They justify a routine Wassermann test when tuberculosis is suspected, especially in early adult and middle life.

22. Myalgia, arthralgia, and bone pain are easily confused with

"rheumatism." The traditional nocturnal character is not a safe guide to syphilis, and is often absent.

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## ON THE PATHOGENESIS AND TREATMENT OF TABES DORSALIS AND GENERAL PARALYSIS

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(Received for publication, March 28, 1922)

THERE are yet many unsolved problems connected with the genesis of syphilitic lesions of the central nervous system and rational methods of treating them; indeed, many elementary questions remain unanswered save by hypothesis. Here are a few of them:

Why, since spirochetes are so few in number, does the excessive production of fibrous tissue in gumma take place? Wherefore the antithesis between the central nervous system and the remainder of the body exemplified in the practical escape of the one when the other is involved? Why do tabes, paresis and optic atrophy, supposedly of similar nature, not occur in conjunction more frequently? What is the genesis of the structural lesions of tabes and paresis? What are rational ways of attempting to improve the treatment of these conditions?

It is not the purpose here to enter into a consideration of all these questions as the limits of one communication will not permit that, but merely to point out briefly a few of the factors entering into the last two. These two questions are of the greatest practical importance and are of necessity studied together if conclusions are to be of any value. Strangely enough, scarcely any program of treatment advocated and followed in recent years has been formulated with the least regard to the origin of the lesion for which it was intended.

The origin of the lesions characteristic of tabes and paresis might appear at first glance to be quite simple, appearing *a priori* to be an infection of the affected regions with the *Spirochete pallida*; but a closer study of the pathology brings out some puzzling relations.

In tabes the primary changes consist in a degeneration of the entering posterior or sensory root fibers at the point in the spinal



cord labelled X in Fig. 1. This fact was established quite conclusively by the studies of Orr and Rows,<sup>1</sup> and other students before and since their time are in complete accord with them. There are no inflammatory changes in the cord hereabouts and there may or may not be in the overlying pia. Spirochetes are not found in the cord and rarely in the pia. The question is why does degeneration

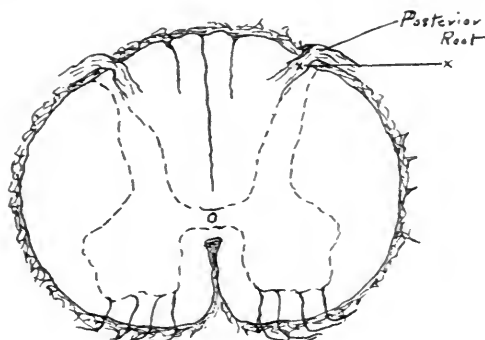


Fig. 1.—Spinal cord.

take place just at this point? It was pointed out many years ago that as the roots pierce the pia, they, and possibly also the individual myelin sheaths, become constricted (Obersteiner-Redlich ring) and also that the neurilemmal or connective tissue sheath is lost. It has been supposed therefore, that this is a vulnerable point and that in tabes either syphilitic toxins or constriction by an inflamed



Fig. 2.—Cortex, paresis.

pia may cause the degeneration. Space does not permit further consideration of these theories or mention of the several others that have been advanced; suffice it to say that each and all of these theories are open to objection.

In paresis the anatomical findings are essentially a moderate general devastation of the cerebral cortex and an accumulation of

mononuclear types of leucocytes about the blood vessels. The changes may be illustrated by diagram (Fig. 2). Spirochetes are found somewhere in the devastated areas in perhaps half the brains examined; but they are certainly not co-extensive with the distribution, or in proportion to the severity, of the anatomical changes. The mysterious features of this picture are (1) that just indicated, viz., the relation of spirochetes to devastation, (2) the practical limitation of the inflammatory exudate to the walls of the blood vessels. The exudate may be almost entirely wanting as in a few very chronic cases and others like the following:

Man of forty-five. Paretic symptoms of a few months' duration. The clinical and serological findings were typical. After a moderate course of treatment consisting of salvarsan intravenously and in addition intraventricular and intraspinal therapy, all serological tests including the gold chloride test and the cell count became normal. The clinical picture did not alter to any great extent; the patient continued to be weak, apathetic and drowsy. He received no further treatment for over six months and the various tests remained negative. Despite this latter fact, he continued to become weaker and more stupid, finally dying from some slight intercurrent affection.

Examination of the brain disclosed surprisingly few changes in the gross; the pia was quite clear and there was little convolutional atrophy. Microscopically there was a mild general devastation but no perivascular exudate. The vessel walls were considerably thickened and stained more deeply than normal.

It is noteworthy in this case that progression occurred despite the negative tests and in the absence of an inflammatory exudate.

Various attempts have been made to explain the puzzling relations in paretic lesions. Undoubtedly there is a barrier between vessels and brain tissue that is passed with difficulty by leucocytes and substances in the blood stream. Salvarsan does not pass it, because Willeox found no arsenic in brain tissue after an intravenous injection.<sup>2</sup> This statement also applies to certain dyes. This barrier may keep back the leucocytes in paresis but it does not so function in the case of tubercle, gumma and abscess. To explain the disproportion between degeneration and spirochete distribution McIntosh and Fildes<sup>3</sup> have advanced a theory of allergy assuming that in consequence of irritation during the secondary stage the tissues become hypersensitive and therefore at later periods succumb to the small amounts of toxins produced by the few spirochetes present. Their conception of the process in paresis is

that it is analogous to that in gumma except for modifications imposed by the structural restrictions mentioned above.

There would be a better chance of clearing up these mysteries were more known of the movement and functions of the cerebrospinal fluid. It cannot be stated, for instance, whether the fluid is constantly under formation and circulation or whether it is relatively stationary and invariable. Becht and Matill whose studies by virtue of their thoroughness take precedence over all others, were unable to settle this question.<sup>4</sup> That circulation is not active is indicated by the fact that fluid removed from various parts of the ventricular and subarachnoid cavity may vary in its reactions. On the other hand many facts indicate the contrary. Again it is not known to what extent the fluid comes in contact with nervous tissue and is concerned in its nutrition. Certain solutions after injection into the subarachnoid space can be followed in their distribution later in microscopic sections; and it is found that they follow blood vessel walls deep into the nerve tissue and diffuse freely through the cortex. Some maintain that this course is that of the cerebrospinal fluid normally and that it carries nutriment to the tissues (Mott) while others believe that experiment alters relations and that normally the flow is in the opposite direction conveying waste products into the fluid of the subarachnoid cavity (Cushing).<sup>5</sup> Judging from the chemistry of the fluid one would conclude that neither view is correct; but there is evidence for both: On the one hand certain drugs produce heightened nervous responses when introduced into the subarachnoid space; and on the other hand, in meningitis no noteworthy reaction is evident in nerve tissues. The question remains open.

It has occurred to the writer that the central nervous changes in both tabes and paresis may be the result of contamination of the cerebrospinal fluid with an irritant, which may be syphilitic toxin or a protein split product. The distribution of solutions introduced into the arachnoidal space, mentioned in the foregoing paragraph, is evidence in favor of this view. Though this distribution may not be that of spinal fluid under normal conditions, still in the presence of a syphilitic infection conditions may be altered. The widespread distribution of the degeneration in paresis and the peculiar limitation of that in tabes are in favor of this view.

It may be here added that the localization of many nonsyphilitic

processes in the nervous system is hard to explain, for instance, those of infantile paralysis and lethargic encephalitis, of which the former involves chiefly the anterior horns of the spinal cord and the latter structures at the base of the brain.

*Treatment.*—In discussing treatment it is necessary to keep the foregoing facts clearly in mind. It is senseless, for instance, to speak of the "cure" of tabes and paresis in the sense of restoration of the degenerated cells and fibers, for regeneration certainly does not take place in the central nervous system. The most that can be accomplished is complete and permanent arrestment of the degeneration. A regression of some symptoms is to be ascribed to some other factor, which very frequently will prove to be the remission of a complicating meningeal or vascular lesion. These yield readily to the usual exhibitions of mercury and salvarsan and according to Head cannot be diagnosed save by the response to treatment.<sup>6</sup> Head decided that the improvement in serological reactions and symptoms that occurred after three large doses of salvarsan was due to the yielding of a meningitis and the resultant positive findings to deeper processes. Most will agree that the meningitis in his cases responded with remarkable facility, nevertheless his conception is probably correct in a general sense.

Whether the true paretic process ever yields in its advance to treatment is a moot point. As mentioned above it seems that salvarsan in the blood stream does not penetrate to the spirochetes lying in nerve tissue and it is a question whether it does when introduced by the intraspinal route. And even if it does in the latter case, it is probably in quantities too small to be effective if no harm results to the nerve tissue. This last factor has been much neglected; nerve tissue may be suffering injury without its being apparent to the clinical observer at the time. Many even maintain that too intensive intravenous treatment is injurious, although others advocate intensive and prolonged treatment.

The Swift-Ellis method of which the primary object was the introduction of antibodies to counteract toxins and destroy parasites and not the introduction of chemicals as many seem to suppose, is theoretically rational even if the central tissues are not reached and should be employed in every unsatisfactory case.

Whatever is best in present methods, the fact remains that at most they give results far short of the ideal; and to improve on them

it is probable that radical departures must be made. It may be that by the time the diagnosis of paresis can be made, treatment will be of no service but still it is better to take a hopeful view. Of present efforts it may be said that they aim too much at the destruction of the parasite, for as already indicated the chances are that in many cases the spirochete is present in comparatively small numbers. Attention should be given to other possible factors in the process such as the hypersensitivity of McIntosh and Fildes or contamination of the spinal fluid by some irritant. The Swift-Ellis method as introducing antibodies into the subarachnoid space is a rational innovation of the type alluded to. Further efforts should be made to neutralize possible irritants in the spinal fluid or to remove them by prolonged drainage. Other etiologic factors such as these must be sought and the attempt made to remedy them.

*Summary.*—This communication is a discussion of the pathogenesis of tabes dorsalis and general paralysis with a view to the bearing on treatment. The attitude is taken that the immediate presence of the spirochete may be of less importance in the genesis of the lesions, from a therapeutic standpoint, than other factors such as a hypersensitivity of the tissues or the presence of an irritant in the spinal fluid; and consequently that the correction of these factors and others like them, as well as the destruction of the parasite, should be considered in devising methods of treatment. Present methods are regarded as giving results far short of ideal and so radical departures are advocated in experimental work.

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## SOME UNUSUAL MANIFESTATIONS OF SYPHILIS

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(Received for publication, April 25, 1922)

### INTRODUCTION

IT HAS been a matter of common clinical experience to note that syphilis may simulate almost any disease condition. The following six patients seen in hospital practice exemplify certain of these unusual manifestations.

1. Syphilis cerebrospinal tertiary with intraventricular hemorrhage. Recovery.
2. Syphilis cerebrospinal tertiary with intraventricular hemorrhage. Death.
3. Syphiloma of pons varolii with recent hemorrhage. Death.
4. Addison's disease, due to syphilitic fibrosis of adrenal glands. Death.
5. Syphilitic fever, simulating typhoid fever. Recovery.
6. Syphilitic meningitis, subacute. Recovery.

### I.

This patient, M. J. L., male, age thirty, was admitted to hospital July 19, 1918 as a meningitis suspect. He was conscious and complained of frontal headache and stiffness of neck, which had existed for 4 or 5 days. Vomiting had occurred once. A history of "soft chancre" in 1913, which left a scar, was obtained. His temperature was 98.4, pulse 84, respiration 24. The pupils were contracted and irregular, the right being larger than left. They reacted promptly to light and accommodation. Fundus examination showed the media clear but fundi congested. The right ear drum showed slight bulging. There was no mastoid tenderness. The accessory nasal sinuses were negative on roentgenogram except some cloudiness of frontals; the mastoids were clear. Petechiae were absent. The systolic blood pressure was 114, diastolic 76. Kernig's, Brudzinski's and Babinski's signs were absent. The knee jerks could be elicited by reinforcement. The leucocyte count varied on successive days from 21,400 to 12,200. Six successive lumbar punctures for drainage, during the following 12 days, revealed bloody fluid. Cultures for organisms were negative. The Wassermann test on blood was plus-minus but two successive Wassermann tests on spinal fluids were found to be markedly positive. All other cultures

of blood and urine were negative, except that albumin was present in slight amount in the urine for a few weeks. Fever occurred varying from 99.4 to 104°, with gradual decline after two weeks. Urinary retention, delirium, rigidity of neck and restlessness persisted for twelve days. Kernig's sign, which was absent early in the course, became very positive about one week after admission.

The treatment for the first two weeks consisted of mercurial inunctions daily, intramuscular injections of mercury biniodide 16 mg. daily, potassium iodide by mouth and one intravenous injection of arsphenamine 0.4. The mercurial inunctions were then continued for a series of 12 more rubs together with potassium iodide 1.0 t.i.d. pc. At the end of one month the intramuscular injections of Hg. biniodide were begun again for a series of 12 injections and an injection of arsphenamine 0.4 was given. The spinal fluid two days before discharge Oct. 19th, was clear. He subsequently received four additional intravenous injections of arsphenamine. Recovery was uneventful from the acute attack.

The clinical diagnosis, because of the prominence of cerebral symptoms, the finding of blood repeatedly in the cerebrospinal fluid, with positive serologic evidence of syphilis was, syphilis cerebrospinal tertiary with intraventricular hemorrhage.

## II.

This patient, B.L.H., male, aged forty-nine, was admitted to the hospital August 3, 1918, with the admission diagnosis of heat prostration. He was stuporous and irrational but in partially rational moments stated that he had been drinking just before his collapse although no odor of alcohol was evident. A history of chancre in 1917 was obtained. His temperature upon admission was 103°, pulse 120 and respiration 28. The systolic blood pressure was 190, diastolic 90. The pupils were contracted and responded but slightly to light. The bladder was emptied involuntarily. The patellar reflexes were absent and there was partial paralysis of the right leg and foot. The urine contained albumin, small granular casts and many leucocytes. Four days after admission the temperature reached 105°, the neck became rigid and Kernig's sign was positive in the unaffected limb. Babinski's sign was negative. A lumbar puncture was made, the fluid being under marked pressure and hemorrhagic in character. The lumbar puncture was repeated the following day, the fluid likewise being hemorrhagic in character and under increased pressure. The temperature varied from 102.8 to 105, pulse 92 to 160. Culture from the spinal fluid was sterile. The Wassermann reaction was markedly positive on spinal fluid, and positive on blood. The delirium and coma continued to the time of death seven days after admission. Necropsy was not performed. The clinical diagnosis was, syphilis cerebrospinal (tertiary) with intraventricular or meningeal hemorrhage.

## DISCUSSION

The subarachnoid space of the cord is continuous with the general ventricular cavity of the brain by means of the foramen of

Magendie, an opening in the pia in the roof of the fourth ventricle. The choroid plexus occupies the lateral ventricle. Hemorrhage may occur from the anterior choroid artery (a branch of internal carotid) or from the posterior choroid artery (a branch of the posterior cerebral).

### III.

This patient, T.G.E., male, age twenty-four, was admitted to the hospital August 24, 1918. The admission diagnosis was tonsillitis, follicular acute. He was sent to the diphtheria-suspect ward but culture for Klebs-Loeffler bacilli was negative. The venereal history showed that gonorrhea had occurred in July, 1917, which lasted until February, 1918. The diagnosis was changed to secondary syphilis, with mucous patches on tonsils, about one week after admission. The axillary, epitrochlear and inguinal glands were enlarged. The blood Wassermann was reported marked positive Sept. 6, 1918. He received an intravenous injection of arsphenamine 0.4 on Sept. 11, with daily mercury rubs (amount not stated). The second intravenous injection of arsphenamine 0.4 was given on Sept. 18. He was discharged, condition improved, on Sept. 22. He subsequently received three injections of mercury salicylate (65 mg. each) (Oct. 5, Oct. 12, and Nov. 5). The blood Wassermann was reported marked positive on Nov. 8. An intravenous injection of arsphenamine 0.5 was given Nov. 26, 1918.

On Jan. 5, 1919, he was again received at the hospital, in a semiconscious condition. His speech was affected and it was impossible to secure any history except that he had been taken ill the previous day with headache and vomiting. His temperature was 97.4°, pulse rate 60. The leucocyte count was 14,300. The systolic blood pressure was 118, diastolic 95. The patellar reflexes were increased and his pupils were equal and reacted to light. There was no rigidity of neck and Kernig's and Brudzink's signs were not present. A petechial rash was absent. Bilateral spastic twitchings and tremors of legs and feet constantly occurred associated with marked ankle clonus. Babinski's sign was markedly positive. Upon lumbar puncture a clear fluid was withdrawn under marked pressure. No meningococci or tubercle bacilli were found. On the following morning, the pupils were constricted and fixed. There was no retraction of head and the neck was not rigid. Kernig's sign was present. The temperature (rectal) was 98.4°, pulse 64. Forty c.c. of clear spinal fluid was withdrawn under marked pressure. Death occurred about six hours later, less than 24 hours after admission. The cause of death from the clinical symptoms was believed to be cerebrospinal syphilis with hemorrhage. On the day after death the examination of the cerebrospinal fluid was completed in the laboratory and revealed a cell count of 307, globulin marked and Wassermann marked positive.

The necropsy revealed bronchopneumonia in stage of early terminal invasion in both lungs. The other organs, with the exception of the brain were ap-



parently normal. A tumor mass was present involving the entire pons varolii. This mass was disintegrated and softened in the center and contained evidence of a recent hemorrhage into the necrotic area. The edges of the mass were not definitely outlined. The pia and dura were not involved. Microscopically, the tumor mass was made up of neuroglia tissue in which hemorrhage had recently occurred, marked endarteritis was present although fibrous tissue change was not marked. The tissue was in many areas infiltrated with round cells. A few giant cells were found. Necrosis had occurred in many areas. The microscopic diagnosis was syphiloma of pons with recent hemorrhage.

#### DISCUSSION

A slow growing lesion such as tumor in the pons may exist a long time without definite symptoms but when hemorrhage occurs grave symptoms of pons destruction become evident. The dorsal portion contains the chief nuclei of origin of the sixth, seventh, and eighth nerves, the posterior longitudinal bundle and ventrally the motor nucleus of the fifth nerve. The pontine syndrome, a complex of crossed paralysis, consists of a paralysis of one side of the face which may include the tongue, some of the eye muscles, the abducens and motor oculi, and of the opposite side of the body. Disease of the pons covering a considerable area may occur without producing any recognized symptoms. An explanation of certain contradictions which may exist can be found in the fact that the pons is the pathway of many tracts between different component parts of the brain, as well as the apparent origin of several cranial nerves, and the termination of many nerve fibers, all of which are contained in a relatively narrow area. The functions of many of these tracts have not been determined. A lesion which involved, as this gumma had done, extending from the dorsal to the ventral border, would it seems, have involved the pyramidal tract and produce symptoms involving the third, fifth, sixth, seventh and eighth nerves, disturbance of lateral movements of eyeballs, indicating lesion of posterior longitudinal bundle, disturbances of sensation (hemianesthesia) due to destruction of the fillet and the ascending root of the fifth nerve as well as motor paralysis due to destruction of pyramidal tract. In addition, it is difficult to see how other symptoms, such as headache, nausea and vomiting and mental disturbance could be so long absent. An alternating hemiplegia (one side of face and opposite side of body) would have established the focal localization of the lesion, although its absence apparently does not mean that disease of pons may not exist.

## IV.

This patient, G. O. S., male, was admitted to the hospital on Nov. 16, 1917. His occupation was that of a farmer. His father, mother, five brothers and one sister were all living and well. He was an alcoholic abstainer and all venereal history was denied. He had suffered no illness except scarlet fever in 1902, and measles in 1910. Two days before admission he noticed symptoms of fever, stiffness of neck and swelling in throat producing dysphagia. There had been no loss of weight. The pharynx was congested, slight conjunctival injection was noted. A brownish pigmentation especially on the abdomen was evident at this time. Symptoms referable to peritonsillar abscess developed but soon subsided. His fever of 102-104° lasted but 48 hours. The clinical record made note of acute iritis 14 days after admission and mentioned that his condition was much improved 10 days later. One week later, or one month after admission, he complained of severe pain in the soles of both feet with tenderness. This was soon followed by pain in branches of the cervical plexus and difficulty in swallowing liquids. Some tenderness existed on deep pressure along the sciatics and over the branches of the brachial plexus, left arm. Weakness and emaciation became a prominent symptom at this time, followed by a short interval of fever with temperature of 104.4° and vomiting. The brownish pigmentation became extensive covering the flexor surfaces of arms, legs and trunk. The urinary examination revealed albumin and a few leucocytes but no casts or blood cells. The spinal fluid was clear, contained no cells or bacteria, and globulin was absent. Blood counts revealed no abnormality other than secondary anemia, blood cultures were negative.

The patient gradually became weaker, emaciation was more marked, due to inability to retain food, delirium developed at intervals until death occurred. The Wassermann examinations of blood and spinal fluid had not, unfortunately, been completed at time of death due to oversight in reports from the laboratory. The clinical diagnosis was peritonsillar abscess right, multiple neuritis, Addison's disease.

At necropsy, the following changes were found:—*Skin*: Marked bronzing, especially marked about genitalia. *Glandular system*: The cervical, axillary and inguinal glands were palpable, the mesenteric lymph glands varied in size from that of a pea to that of a bean. The adrenal glands were less than one-third the normal size, the right being smaller than the left and contained multiple pin-head to sago-grain sized areas of yellowish gray color. Upon section no normal appearing adrenal tissue could be seen in either gland. The aortic, sacral, and coccygeal glands were moderately enlarged. The thymus appeared completely involuted. The thyroid and parathyroid glands were of normal size and consistency. The hypophysis was slightly pigmented but otherwise appeared normal. *The anatomical diagnosis was as follows*: Fibrosis and atrophy of adrenal glands; moderate hyperplasia and fibrosis of the aortic, carotid, sacral, coccygeal lymph glands and of the entire lymphoid structures in general; marked emaciation and bronzed pigmentation of skin of body; atrophy of myocardium; chronic interstitial pancreatitis; slight interstitial nephritis; fatty metamor-

phosis of liver; hyperplasia and anthracosis of peribronchial lymph glands; acute catarrhal tracheobronchitis.

Microscopic examination of tissues, made through the kindness of Dr. Aldred S. Warthin of the University of Michigan, to whom I am indebted for the report, revealed the following: *Pancreas*: Chronic interstitial pancreatitis and atrophy. Pancreatitis is scattered. Islands many, small; no hyaline ones, although some show fibrosis. Old syphilitic pancreatitis. *Right Adrenal*: Syphilitic inflammation and fibrosis. Very little adrenal tissue left. Medulla completely destroyed. Small islands of cortical cells. *Left Adrenal*: A more active syphilitic inflammation with more cortical tissue preserved. Medullary portion completely destroyed. Marked plasma cell infiltration. The primitive fat lobules outside the adrenals show marked hypertrophy and pigmentation of the fat cells, many of the cells resembling adrenal cells. The periadrenal ganglia show fibrosis, degeneration of the ganglion cells with absence of chromaffin staining. *Liver*: Atrophy with marked peripheral fatty infiltration. Chronic passive congestion. Increase of stroma. Early cirrhosis. *Spleen*: Atrophy. Chronic passive congestion. Moderate sclerosis of arterioles. *Kidney*: An early interstitial nephritis. Marked congestion. *Carotid Body and Glands*: Lymph nodes. Lymphoid hyperplasia. Also contains portions of atrophic thymus with many corpuscles of Hassall and a parathyroid. No chromaffin tissue in parathyroid but it is somewhat hyperplastic. Two types of cells well differentiated. No carotid gland. *Aortic and Sacral Glands and Coccygeal Body*: Lymph nodes and hemolymph nodes showing some lymphoid hyperplasia and fibrosis; and one large ganglion showing a few ganglion cells with chromaffin staining. No coccygeal gland found. *Hypophysis*: Shows no changes. *Heart*: Atrophy of muscle. Perivascular thickenings. No active syphilitic areas found.

#### DISCUSSION

The syphilitic fibrosis of the adrenals was the cause of the clinical picture known as Addison's Disease. Tuberculous destruction may also produce a similar condition. In the left adrenal the syphilitic process was active, the medullary portion being completely destroyed. Marked plasma cell infiltration was present. There were no gummatous changes in the adrenals. The interesting observation was made that in the primitive fat globules around the adrenals there was apparent formation of chromaffin cells out of the fat cells, a condition which may occur in cases of extreme cachexia. In the ganglia, the parathyroid and hypophysis there was almost entire absence of chromaffin tissue. It unfortunately was impossible to state whether the disease in this patient was acquired or congenital. The iritis should have caused our more active suspicions of a luetic process.

## V.

P. F., male, age eighteen, was admitted to the hospital August 16, 1920. His complaint was fever and chills, severe headache with vomiting, diarrhea and pain in the abdomen all of which had existed for three days. His temperature was 103°, pulse 110. Marked tenderness existed over the gall bladder and epigastrium, the leucocyte count was 16,200. He was tentatively marked for observation for "acute abdominal condition, probably requiring surgical intervention." The spleen was not enlarged. Sordes were present, the abdominal muscles were rigid and no rose spots were found. A blood culture taken on the day after admission reported *Staphylococcus albus* (probable contamination). The sputum was blood streaked and contained many pneumococci (type not determined) and staphylococci, but no tubercle bacilli. His blood Wassermann was reported positive. Widal agglutination tests with Eberth bacillus and paratyphoid A and B were negative. No parasites or ova were found in the stools. Urinary examinations were repeatedly negative for abnormal ingredients. Blood examinations revealed moderate secondary anemia. R. B. C. 3,960,000; W. B. C. 16,000; polymorphonuclears 77 per cent; eosinophiles and malarial parasites absent. Hb. 65.

Further examination revealed normal cerebation but moderate somnolence from which he could be easily aroused. There were no signs of an intracerebral lesion. A moderately loud diastolic murmur was present over the precordium, the point of maximum intensity being over the pulmonic area. The heart dullness was not increased to right or left and there was no evidence of decompensation. The B. P. was 110/60. The fever, which was of a continuous type, reached 102°-103° daily. A diagnosis of endocarditis was considered at this time but the blood cultures were repeatedly negative. Pyelitis was excluded. Lethargic encephalitis was also considered, because of the patient's somnolence, but neurologic signs were absent. Quinine was administered to physiologic effect as a therapeutic test for latent malaria without effect upon the fever. Mercuric biniodide injections of 10-15 mg. were given daily beginning on the ninth day after admission. These were continued until the twenty-first day with but little effect upon the fever. An intravenous injection of neoarsphenamine 0.45 was given on the twenty-first to twenty-fourth days. The fever promptly subsided. During the following month of observation six more injections of neoarsphenamine in doses varying from 0.45 to 0.9 were given before discharge from the hospital. His blood Wassermann at that time was one plus.

## DISCUSSION

The clinical diagnosis was syphilitic fever simulating that of typhoid for over 4 weeks. There were no clinical evidences or history of syphilis other than the markedly positive blood Wassermann reaction. The fever was not influenced by injections of mercuric biniodide in moderate doses but prompt reduction of fever occurred upon the intravenous injection of neoarsphenamine. The frequency

of fever during the course of syphilis is variously estimated (Osler and McCrae: *Modern Medicine*, Vol. II, pg. 159). The vast majority of cases are afebrile throughout the course of the disease except during the stage of invasion when various estimates give the proportion of cases with fever at 25-35 per cent. The fever is usually slight at this time. At times during the invasive stage the fever curve may simulate typhoid fever and Fournier has described the condition as "typhose syphilitique." The fever which may accompany the tertiary manifestations may be much more confusing. Osler has stated "the profession scarcely realizes that protracted fever of almost any type may occur in tertiary syphilis." It is difficult to understand why fever may be present in some and absent in others. The liver or some other abdominal organ may be involved. In the patient under consideration the symptoms leading to hospital admission were such as to arouse suspicion of an acute surgical condition.

#### VI.

E. S., male, age twenty-three, was admitted to the hospital Sept. 9, 1920. His main complaint was severe headache, rigidity of the neck, blurring of vision and diplopia, difficulty in swallowing and regurgitation of food and water. There had been a loss of 30 pounds weight in 6 months. In March, 1920, a sore on glans lasting 3 weeks had occurred coincident with gonorrhea. The Wassermann test was reported positive at this time and he had had ten intravenous injections or arsphenamine, ten intramuscular injections of Hg. and some Hg. inunctions. I am indebted to Dr. Geo. D. Maner, then interne on the Service, for the following abstract of the examination: the pupils were unequal but reacted to light and accommodation, photophobia, strabismus or ocular palsy were absent. The eye grounds were hazy, the disk edges indefinite due to swelling, the veins were distended and appeared broken at the margins due to choked disk. The neck was rigid and retracted. The abdominal reflexes were hyperactive, the patellar reflexes diminished. Ankle clonus, Babinski and Kernig signs were negative. The temperature was 100°. The urine contained a few hyaline and granular casts and many leucocytes. The spinal fluid pressure was not increased but was cloudy, due to the presence of many cells. A differential count of these cells showed mononuclear lymphocytes 59 per cent, polynuclears 31 per cent. No organisms were found on culture but globulin was present and the Wassermann examination was reported marked positive. The blood Wassermann was also reported marked positive. The leucocyte count was 20,700 of which the polynuclears were 85 per cent. The patient soon became stuporous. There was increasing difficulty in swallowing due to paralysis of muscles of deglutition. A second lumbar puncture showed the fluid under increased pressure, the cell count was 750 per c.mm. of which 72 per cent

were small mononuclear lymphocytes and 10 per cent large mononuclear lymphocytes. Nasal feedings were begun. Neoarsphenamine 0.6 was injected intravenously and fifteen minutes later 30 c.c. of spinal fluid was withdrawn. The cell count was 1,000 per c.mm., globulin markedly increased, Lange colloidal gold test gave a luetic curve. Mercury biniiodide injections in doses of 16 to 21 mg. were given intramuscularly. The intravenous injections of neoarsphenamine 0.9 were repeated every two days, followed by lumbar drainage of 30 c.c. of fluid. Swelling of the optic disk began to slowly subside after the second injection, as did also the fever. After the third injection semisolid foods could be swallowed, the stupor was less marked and the rigidity of neck and headache began to disappear. The spinal fluid cell count rapidly diminished from 1,000 to 200 to 70 in one week. The diplopia continued, and at intervals horizontal nystagmus was present for about two weeks. During the course of the next month his progress was rapid. Muscular control returned, the pupils became equal, the vision steadily improved, and most of the clinical evidences of the condition disappeared with the exception of a slightly positive Romberg. He received a total of 5.1 gms. neoarsphenamine in six injections during fourteen days. He also received 14 injections of Hg. biniiodide, 16 mg. each, and 18 injections of 21 mg. each, a total of 0.6 Hg. biniiodide. He was discharged two months after admission clinically improved but his blood Wassermann was still markedly positive. The clinical diagnosis was syphilitic meningitis.

#### DISCUSSION.

In syphilitic meningitis the lesion is usually limited to the base of the brain. In such instances the optic and oculomotor nerves will be involved. The abducens and trochlear nerves are more rarely affected. Frequently ptosis is the only symptom of third nerve involvement, or the branch controlling the pupil may be affected producing pupillary rigidity, which is commonly unilateral. Neuritis of the optic nerve may be present, or a typical choked disk may occur followed by atrophy. When the process extends to the posterior portion of the brain base the seventh and eighth nerves are usually involved. The facial paralysis is of the peripheral type. Involvement of the eighth nerve produces nerve deafness and vertigo. The symptoms may vary from day to day. As Grinker has stated (Forehheimer's Ther. of Int. Dis., 1914, iv, 474) "the most typical and constant factors in syphilis are atypicity and inconstancy."

## PRACTICAL OBSERVATIONS ON SYPHILIS. III\*

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(Received for publication, March 15, 1922)

### SYPHILIS OF THE VASCULAR SYSTEM

AS FORDYCE has insisted, and as I have attempted to point out, syphilis is primarily a disease of the blood vessels. Even in the chancre the primary lesion is an endarteritis and a panarteritis. This is true in all other stages of syphilis, the lesions usually beginning in the perivascular lymph spaces. A granuloma speedily results, a granuloma characterized by the presence of small mononuclear and plasma cells, with a formation of new capillaries and fixed connective tissue elements. Giant cells may be found. Gumma formation is simply due to a breaking down of the tissues because they are less resistant to the action of the treponema. When one remembers these facts it is not surprising that syphilis of the vascular system is daily becoming more important.

### SYPHILIS OF THE HEART

It is becoming a matter not only of clinical but also of autopsy record that the heart is frequently involved in syphilis. Fifteen years ago Grossman wrote that in 288 cases of secondary syphilis marked disturbances of rate and rhythm occurred in 85 per cent and murmurs in 40 per cent. Practically all observers are agreed that aortic insufficiency is most often caused by syphilis, and Warthin has shown that syphilis plays a great part in the production of myocarditis. Autopsy records bear out the clinical findings remarkably well. Symmers has performed autopsies upon 314 cases of late acquired lues and has found that the aortic valves were sclerotic in sixty-four instances, which figures agree closely with those of Longcope. Harlow Brooks in 50 consecutive autopsies upon syphilitic patients with heart disease found that the pericardium was diseased 28 times, the myocardium 44 times, that true cardiac

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\*Through an error the illustrations intended to accompany this text were printed in the preceding section in the April, 1922 issue.

gumma was present 5 times, and that in 35 instances disease of the coronary arteries was present.

The syphilitic changes in the heart may be classified as follows: Pericarditis; myocarditis; endocarditis; valvular disease; disease of the coronary arteries, angina; cardiac aneurysm; heart block.

*Pericardial Syphilis.*—Opalescent patches of thickening appear at the perforation points of the terminal arterioles. Adami and Nicholls state the "milk-spots" are found in 14 per cent of all autopsies, and that they are merely the results of intermittent pressure.

*Myocardial Syphilis.*—While clinically it is rather unusual to find marked early cardiac disease, yet such may occur; only recently I have seen a case in a physician where a serious myocarditis developed even before the secondaries became manifest. Clinically the manifestation may appear either in the course of the secondaries or late in the course of the disease. Anders and Brooks have well described the condition found upon clinical examination. If the disease develops during the secondary stage, the principal features are arrhythmia, particularly intermittence and tachycardia, and at times extrasystoles. The irregularity becomes more marked after mild exercise or through nervous fear. Precordial pain is not common, and various writers disagree as to the amount of dyspnea present. Cyanosis frequently occurs. These manifestations are not characteristic of syphilis, as they may occur in any other form of myocarditis. However, they will usually disappear if antisyphilitic medication be pushed. In the late stages of syphilis the manifestations are those of myocarditis due to other causes. While the condition is difficult to diagnose in the absence of a positive Wassermann, Anders states: "Certain clinical peculiarities already mentioned may, however, serve to arouse suspicion of syphilis. Of these the tonelessness of the first heart sound and the decidedly irregular, accentuated character of the arrhythmia deserve special mention."

*Syphilitic Endocarditis and Valvular Disease.*—Over 75 per cent of all cases of aortic insufficiency occur in syphilitics. On the other hand, it is probable that syphilis but rarely causes other forms of valvular trouble. The mere fact that a patient has complained of rheumatic pains is no reason for making a diagnosis of rheumatic origin for a heart lesion; syphilis frequently causes arthritic symptoms.

*Diseases of the Coronary Arteries.*—Brooks states that in 50 autop-



sies performed upon syphilitic heart patients he found that in 35 instances the disease of the coronary vessels was greater than the general arterial disease. "From the diseased vessels there spreads out into the muscle all sorts of changes, from a granulomatous and true myocarditis to fibrosis and necrosis, the result of deficient nourishment." The symptoms are similar to those described in the section upon myocarditis, except that there may be rather more pain.

*Angina.*—Anders states that he has collected 270 cases of angina pectoris from the literature, of which 72 gave evidence of syphilis. Anders continues: "This percentage, however, is much too small, since in 250 of the recorded instances no mention was made of a Wassermann test, sole dependence being placed in the history." Osler considers it an important cause, especially in persons under forty. In these days when angina has become such a fashionable disease, it is nothing less than criminal for physicians to neglect the possibility of syphilis.

*Heart Block.*—The condition known as heart block or Stokes-Adams' disease is due to the failure of the ventricle to contract each time that the auricle does. This is because the bundle of His fails in its conductivity. That this failure may be due to syphilis of the bundle has been definitely established by many men.

*Aneurysm of the Heart.*—Aneurysm of the heart wall is unusual, but does occur, as Brooks has found it in three instances out of fifty autopsies upon patients with syphilitic heart lesions. Hence syphilis is probably the commonest cause, if not the only cause, barring trauma, of this disturbance. Osler states that the left ventricle near the apex is the usual seat of aneurysm. Ultimately a large rounded tumor may protrude from the side of the heart wall.

*Treatment of Syphilis of the Heart.*—I know from personal experience that such patients bear intravenous injections well. Personally, I administer about two-thirds of a full dose about every week, while mercury is given in full doses by intramuscular injection. In urgent cases the arsphenamine may be given even more frequently. A competent internist should always have charge of such a patient, and direct the medication for the heart condition itself, for digitalis or some other of the cardiac stimulants may frequently be employed to advantage.

*Aortitis.*—That many syphilitics suffer from aortitis is made mani-

fest by the autopsy experiences of Symmers, who found that in autopsies performed upon 314 cases of late acquired syphilis, aortitis was found in 175 instances. In this series the arch alone was affected 109 times, while the entire aorta was diseased 49 times, with combined lesions in 29 instances. Other pathologists recognize the condition as an extremely common one, ranking with heart, testicle and adrenal lesions in frequency.

The lesion usually develops before the patient is fifty years of age, the average age being a little over forty. The symptoms which have attracted the attention of every writer on the subject are pain, dyspnea, palpitation and tachycardia. The patient usually complains of a dull, either constant or intermittent pain beneath the sternum. However, anginal pains are far from uncommon. In most of the cases there is dyspnea upon slight exertion, and this often becomes worse, especially if aortic insufficiency supervenes as it is so apt to do. In other instances the dyspnea may be paroxysmal in character, coming on in attacks which may last from five to fifteen minutes. The dyspnea is prone to be expiratory in character. In some few instances aortitis may cause a continued fever as Popoff has pointed out. By some cyanosis is said to be common.

The commonest complications are aortic insufficiency, angina pectoris and aneurysm. As already pointed out, aortic insufficiency is an extremely common complication, in fact it may be looked upon as the natural result of practically all cases of aortitis. Probably from one-fifth to one-sixth of the cases develop an aortic dilatation, often sufficiently large to be called an aneurysm.

In making the diagnosis the symptoms are of great importance. Next ranks a positive Wassermann reaction, at least in cases that do not show a dilatation of the aorta. Where the aorta is dilated, x-ray examination is of the greatest possible assistance, although some care must be used in interpreting the shadows.

The demonstration of the presence of treponemata in the lesions by Benda, Reuter, Schmorl, Wright and Richardson and Longcope and Cook has settled any possible question as to the syphilitic nature of these lesions, even although Symmers, Crowell, Aschoff and Brown have failed to find them. In addition Fordyce has proved that the histopathologic picture is unmistakably that of syphilis. The disease begins in the adventitia, but the most striking changes are in the media. Miliary gummata are first formed,

these undergo necrosis, and are replaced by scar tissue. In fresh cases there may be found about the vasa vasorum of the adventitia an inflammatory exudate of lymphoid and plasma cells; the nutrient vessels themselves undergo an obliterative endarteritis. The elastic tissue is neither fragmented nor entirely absent. The intima either shows no change or a compensatory thickening. It is still a disputed question as to whether or not the changes are primary in the media or in the vasa vasorum.

Unquestionably all cases suffering from late syphilis, either active or latent, should have a study made of their aortas. In this way much trouble could undoubtedly be averted. Whether or not there are any symptoms, a fluoroscopic or radiographic examination should be made.

#### PERIPHERAL ARTERITIS

When one considers that syphilis of the aorta and of the cerebral vessels is so common, he must be surprised at the paucity of the authentic literature dealing with syphilitic arteritis of the smaller vessels. In the literature there is still great confusion, for the lesions produced by such disturbances are very similar to those found in Raynaud's disease and in thromboangiitis obliterans of Buerger. That syphilis can affect other arteries than those above mentioned is definitely proved and the presence of aneurysms of various arteries also bears out this statement. In the peripheral types of arteritis the lesions would naturally be due to disturbed circulation, and would consist of either anemia or possibly cyanosis, according to the extent of the lesions and the quantity of the peripheral circulation. Gangrene would naturally result in the severe cases.

#### RAYNAUD'S DISEASE

As already indicated in the preceding section on syphilitic peripheral arteritis, the greatest confusion exists in the literature between Raynaud's disease and syphilitic arteritis. Lissner has recently completely reviewed the subject of Raynaud's disease due to syphilis, and has given a full bibliography to date.

For years there has been a feeling among some clinicians that syphilis is responsible for certain cases that show symptoms that are almost absolutely characteristic of Raynaud's disease. I have

had one apparently typical mild case where all of the lesions promptly subsided after the administration of arsphenamine. Lissner states that he cannot feel that the definite proof has been advanced that Raynaud's disease may be due to syphilis, although there is a mass of evidence that makes this view extremely suggestive. He says that there are three possibilities, one, that there may be a definite syphilitic lesion of blood vessels or of the nerve supply to such vessels, two, that the symptom-complex may be due to syphilitic toxins, and three, that the bodily resistance may be so lowered by syphilis that the individual may be more susceptible to Raynaud's disease.

#### ANEURYSM

Inasmuch as the thoracic aneurysm is the one that most concerns syphilographers, and inasmuch as it should be diagnosed at an early period, I shall confine the description of the clinical course to this one variety. There are two common types, the diffuse, which is due to a general dilatation of the walls of the aorta, and the circumscribed, which is due to a giving away of the wall in one portion only. Aneurysms are most common in the ascending aorta and in the arch. In the former type, the physical signs are usually rather more pronounced than are the symptoms. A pulsation may be seen in the second or third interspaces, and this may be palpated as well, together with a thrill and diastolic shock. At times percussion will outline the mass. An aortic systolic murmur is common.

In regard to the treatment of aneurysm there are two points to be emphasized. In the first place the local damage to the vessel must be treated as outlined in the various works upon medicine. In the second place the syphilis should never be neglected, for while the aneurysm cannot be cured, at least in the majority of instances, the patient can be rendered much more comfortable. At times this may be distinctly dangerous, for a man may feel that he is well enough to resume active work, when such is not the case. Personally I give arsphenamine in about 0.4 gm. doses, employing a sufficient number of injections to render the Wassermann negative. It is amazing how much more comfortable the patients can be made. This would seem to indicate that the pain is frequently due to the syphilitic process rather than to pressure. Mercury

should always follow up the arsphenamine. The more I see of antisyphilitic treatment in aneurysms the more enthusiastic I become over the temporary relief.

#### ARTERIOSCLEROSIS AND HYPERTENSION

The question as to the etiologic importance of syphilis in either arteriosclerosis or hypertension is still far from being a closed book. We must keep open minds on the whole question.

#### SYPHILIS OF THE VEINS

Hoffmann distinguished three forms of venous syphilis, the diffuse thickening of a vein, the nodose thickening and the erythema nodosum syphiliticum. Hutchinson has described a fourth form of periphlebitis. In the first form, which may occur either during early or late syphilis, a vein may be involved for practically its whole extent, or for only a portion of its length. Either a deep or superficial vein may be affected, and the swelling may be either uniform, or more frequently irregular in different portions. There are always present the characteristics of inflammation, namely, swelling, heat and pain. Pathologically both the venous and perivenous structures are involved by a diffuse syphilitic process. The second type is similar; the whole vein is not affected, only various portions of it. In the third type the eruption simulates erythema nodosum, the nodules usually lasting but a few days or weeks. As regards the variety described by Hutchinson that author states: "There is a curious form of periphlebitis due to syphilis which is often very chronic in its course, and produces very peculiar changes. It is attended by great thickening around distended and convoluted veins, which become matted together in a cake-like mass, and adherent to the skin. Sometimes suppuration occurs and portions of cellular tissue slough, producing characteristic sores, but in other cases the condition may last, in a state possibly of partial cure by specifics, for many years. It always tends to spread. Slight forms of syphilitic periphlebitis are not uncommon and are usually seen in the legs."

#### BLOOD CHANGES IN SYPHILIS

*Red Blood Cells.*—In the vast majority of instances there is but little change in the number of the red blood corpuscles early in

the course of the disease, although women may show a drop of 20 to 25 per cent. In late syphilis there may be an extreme anemia, a reduction in the cells and the hemoglobin, the color index usually being low. Muller, Weicksel and others have reported cases of pernicious anemia as being due to syphilis. Referring to this point Emerson states: "In hereditary and tertiary lues the red blood cells are seriously affected, in number, size and color. Megaloblasts are common. The blood picture, especially of the long-standing cases with much scarring of the organs and the sclerotic bone marrow, resembles primary pernicious anemia."

*Hemoglobin.*—It is generally agreed that early in the course of syphilis, before the rash has appeared, there is a marked reduction in the amount of hemoglobin. In the European clinics great stress was formerly placed on the value of this fact, especially in diagnosing chancres in women. Quite frequently if a large inunction or injection of mercury be given just before the development of the rash there is an immediate drop of from 10 to 20 per cent in the hemoglobin, and then a rise to normal. Justus has taken advantage of this fact to develop a test which he claimed as specific for syphilis.

#### SYPHILIS OF THE SPLEEN

Wile examined one hundred cases of primary and of secondary syphilis and found splenic enlargement in thirty-six. The spleen was hard and firm in seventeen cases, soft in three and tender in six. The majority of the cases showed marked impairment of the general health. The enlargement may occur before the eruption appears. The enlargement tends to disappear under treatment, but like other hypertrophies of lymphoid tissue may persist for a considerable space of time.

Osler states that four types of splenic lesions may be found in late syphilis. Gummata are the most common; they have been well described by Wilks. They may be either single or multiple, large or small. They are often associated with gummata of the liver. Perisplenitis may exist in the form of a thickened capsule. Cicatrices may result from old gummata, and the spleen resemble an old syphilitic liver, in that scars and depressions are marked. Amyloid changes may occur in long-standing cases, especially where the bones or liver have been seriously affected. They may be con-

finer to the Malpighian bodies, or the process may be diffuse. In some instances leucemia may be simulated, both by the physical and by the blood findings.

Clark and Neuberg have both reported instances where splenic anemia was closely simulated, and it is more than probable that certain cases of Banti's disease are due to syphilis, either congenital or acquired.

#### SYPHILIS OF THE LYMPH NODES

Friedlander has written the best article upon the clinical value of the lymph gland examination in syphilis. He finds that unilateral enlargement has but little significance, but that the bilateral enlargement of certain groups is of considerable importance. For instance, he found the epitrochlear glands an average of 77 per cent enlarged in syphilis, and but  $27\frac{1}{2}$  per cent in nonsyphilitic conditions, and of the occipital 82 per cent inluetics and 45 per cent in other patients, and of posterior cervical 84 per cent in syphilitics and 47 per cent in the nonsyphilitics. It is a well-known fact that in the negro race glandular enlargement is more frequent and more pronounced than in the white. In late syphilis glandular enlargement is not so constant as in the earlier stages of the disease. Two points should be especially noted, first that universal glandular enlargement is very suggestive of syphilis, and second that enlargement of submammary lymph nodes is also extremely suggestive.

Late in syphilis gummous changes in the glands are occasionally met with, much more frequently in the negro than in the white.

### Section 12

#### SYPHILIS OF THE BONES, JOINTS, MUSCLES, TENDONS, AND BURSÆ

##### SYPHILIS OF THE BONES

*Localization.*—For many years, nodes on the crest of the tibia have always made us suspect syphilis, but without impressing us with the importance of such a phenomenon in relation to general or localized bone syphilis. A few of the percentages taken from the literature are of interest in this respect. Gangolphe and Perret, in 48 cases of bone syphilis, gave the following localization: femur

26, humerus 28, tibia 18, radius 10, sternum 3, clavicle 16, patella 1, radius 3, forearm 2, scapula 4.

Jullien in 64 cases, gave the following: nose 19, tibia 15, palate 15, sternum 5, clavicle 4, maxillary 4, frontal 1, parietal 1, vertebra 1, scapula 1, forearm 1, knee-cap 1.

Fournier, on the other hand, showed that of all of the involvements, the tibia was affected in 26.3 per cent, nasal palatal skeleton in 25 per cent, and the cranium in 19 per cent.

A. *Periostitis and Osteoperiostitis*.—Periostitis is a swelling of the periosteum or subperiosteal marrow, and is caused by a true primary vascular change. This swelling interferes with the bone, thus causing the pain characteristic of this form of disease. The osteoperiostitis is an extension of the disease into the bony tissue, that is, the Haversian canals. These inflammatory processes may end by resolution, especially under treatment, or they may progress to a rarefying osteitis or to a proliferative osteitis, the latter causing an eburnation or formation of osteophytes or exostoses. Rarefying osteitis progresses by destroying the walls of the Haversian canals producing a spongy condition of the bone which may or may not be filled up by bone proliferation. If not, necrosis is the result. Suppurating periostitis is the result of a secondary infection involving the injured tissues.

B. *Gummous Lesions*.—Gumma is the typical lesion of the tertiary period, and is the end result of the proliferative changes of the inflammatory period, that is, as the inflammation advances and the fibrous elements become more dense and contracted, the blood supply to the center cells becomes gradually diminished. There is a degeneration of the central cells and finally a background of granular matter is the end result of this degeneration. As a result of this, the center of the tumor softens, and gradually caseates while the periphery preserves its normal appearance. In the bones gummata evolve as in any other tissue, and may be found wherever the inflammatory process previously described has existed. Gummata of the bone may be periosteal, subperiosteal, osseous, or osteomyelitic. The gummous destructive processes, as we might expect, are more extensive than the destruction accompanying the true inflammatory lesion.

*Lesion of Special Bones.—Long Bones*.—The diaphysis is usually increased in size, the periosteum thickened and adherent. The in-



crease may be localized either globular masses or a spindle-shaped tumefaction. The contour of the entire bone may be changed, especially noticeable in the tibia, producing the so-called saber-shaped tibia, a frequent occurrence in congenital syphilis. At times large portions of bone are so involved and increased in size that the normal contour is very much changed. Observations of this character have been noted in the femur which has assumed the shape of a cudgel. The clavicle is another example where an entire bone may become two or three times its normal size.

*Short Bones.*—The phalanges are frequently perforated or parts may entirely disappear causing a shortening, or there may be typical periostitis with surface roughening.

*Flat Bones.*—As before stated, the cranium, especially the anterior vault, is frequently the seat of destructive processes, and there are numerous examples in the museums where large surface areas have been eaten away, or complete perforations have taken place as though produced by a bullet. The sieve-like formation is rather the common observation, the holes completely penetrating the skull. The bones of the face are a favorite seat of syphilitic destruction, especially the bones of the nose, producing the so-called saddle nose.

*The Spinal Column.*—There may be a simple inflammatory periostitis or gummous lesion. If a periostitis, it resembles periosteal thickenings due to other infectious agents. If a gummous lesion, it attacks any portion of the vertebra, but as a rule, the vertebral body is alone attacked. If the latter, the spindle-shaped portion of the bone is transformed into a soft yellowish detritus or even a purulent liquid. It may not proceed to this degree, rarefaction being the most noted change. Breaking down of the vertebral bodies under this condition due to the superincumbent weight is possible, such as is seen in the early or slowly developing tuberculous lesions. The more dense portions of the vertebra, the posterior arches, and the processes may also be attacked. The process may also extend to intervertebral discs and the surrounding ligaments.

*Clinical Study.*—Spillman states that there are two never-failing signs of bone involvement: first pain; second, tumefaction; and that there are two negative signs: first, absence of suppuration; second, absence of glandular enlargement corresponding to the lesion. The pains vary but are often extensive and lancinating. They may

come and go, almost always appearing at night and are a most important diagnostic sign of bone syphilis. They jump from one part of the body to another resembling so-called rheumatic pains.

*Tumefaction.*—The more superficial the bones, the more apt they are to be found involved. This may be due to the fact that they suffer traumatism more readily, or it may mean that the deep-seated bones are more difficult of examination. In the cases of periostitis, a spindle-shaped swelling is the rule, either localized, or involving a large part of the bone. Usually the radiographic findings show single or multiple periosteal thickenings. Often the entire bone is thickened, especially the cortical layer, if the disease is of long duration.

There is often a roughening of the surfaces of the bone which may present definite exostosis. If the condition is a gummous involvement, nodular areas may be made out, single or multiple, their consistency depending upon whether the gumma is firm or has undergone degeneration. Unless the overlying tissues have become involved, they remain normally clear and the local temperature is normal. If, however, a gumma has extended or has broken down and is suppurating, the surface shows signs of local irritation, that is, a reddening or bluish reddening of the surface with a slight rise of temperature. Should such a process go on, ulceration is the result. If, however, regeneration takes place, a subcutaneous scar results which is rather peculiar to syphilitic lesions.

The sternoclavicular junction is also a favorite seat of the disease. A number of observers have called attention to sternum cases. Two very striking examples are reported by Schulman, of New York. In both instances, the patients complained of heart pain. Careful examination in each instance disclosed a small area of exquisite tenderness over the sternum.

Syphilitic dactylitis is of special interest because the ease of observation is important in suggesting a diagnosis. Periostitis is the more frequent type, while necrosis of the bones as the result of a gummatous condition is of rare occurrence. Portions of the bone may be destroyed, giving much the same x-ray appearance as is seen in chronic gout, that is, a punched out area in the shaft of the bone. Large portions of the shaft may entirely disappear and a shortening of the extremities results.

The symptomatology of syphilis of the spine does not differ essentially from that of other affections of the spine, and consists especially of pain, tenderness, rigidity, and deformity. When the vertebral body is destroyed, the symptoms are not unlike those of Pott's disease, but the kyphosis which is so characteristic of Pott's disease is comparatively rare. This is due to the much less extensive destruction of vertebral bodies in syphilis. One observer states that in syphilis of the spine, one vertebra only was involved in 40 per cent of the cases. The attitudes assumed in spinal syphilis are not unlike those of true Pott's disease, that is, those attitudes due to a stiffness of the spine.

#### SYPHILIS OF THE JOINTS

Many articles upon the subject have been written, two of the most complete being the theses of Gouriantz and Pillon.

*Frequency.*—Even yet it is a bit uncertain as to just how frequent this form of syphilis is. Every clinician knows that a high percentage of all syphilitics at some time suffer from arthralgias. Wile and Snear have studied 165 cases of early syphilis and have found that 60 of these cases showed either bone or joint involvement, in 21 instances the joints alone being involved, while in 12 both bones and joints were affected. Baets reports that out of 100 cases of arthritis seen in the Canal Zone no fewer than 63 were of syphilitic nature. Other observers have reported that from 10 to 40 per cent of all syphilitics have some joint involvement.

Clark, writing in the *Journal of the American Medical Association* for Dec. 18, 1918, reports that in the Canal Zone 1100 consecutive autopsies have been performed and the joints examined in each instance. In 172 of these cases definite joint lesions were found, although less than 1 per cent of the total number of postmortems were done upon "arthritis suspects." In 96 instances the arthritis was due to syphilis. In this series the right knee was involved 90 times, the left knee 92 times, the right hip 17, the left hip 9, right shoulder 17, left shoulder 8, right elbow 2, left elbow 2, right ankle 2, left ankle 3, and the right wrist and spine once each. This would seem to prove conclusively that syphilitic arthritis is much more frequent than we have been led to believe from the reports of the past, and that it is frequently present although it gives no clinical symptoms.

*Time of Involvement.*—Wile and Senear have definitely shown that during either the primary or secondary stage about 20 per cent of all cases show some symptoms referable to the joints. During the late stages of syphilis less than 5 per cent of all patients complain of arthralgia and an even smaller number have some more serious lesion.

*Clinical Types.*—After considerable observation and a careful reading of all available literature, we feel that in acquired syphilis the following clinical types can be recognized:

- In early syphilis,
  - Arthralgia.
  - Synovitis—the pseudorheumatism of the French authors.
  - Hydrarthrosis.
- In late syphilis,
  - Arthralgia.
  - Synovitis.
  - Hydrarthrosis.
  - Osteochondroarthropathies,—the pseudowhite swellings of the French.
  - Gummous perisynovitis.
  - Charcot's joint of tabes.

In addition there are two other types which deserve brief mention, although we are not yet justified in classing them as clinical entities—namely, the pseudoarthritis deformans of Mericamp and the hybrid forms of Weliaminoff.

*Arthralgia.*—The arthralgias are the simplest and most frequent joint lesions of syphilis. Gouriantz estimates that they affect about 8 per cent of all syphilitics, but many observers give a higher figure. They occur early in the course of the disease, usually with the early rash, but sometimes with the chancre. Any joint may be affected, but those most frequently involved are the large ones, namely, the shoulders, knees, wrists and ankles. The pain may be either mono- or poly-articular and is usually worse at night. The symptoms are entirely subjective, there are absolutely no objective signs, and in several cases which we have had radiographed no joint abnormalities could be detected. Ordinarily the pain is increased on some particular movement, but sometimes is eased by movement. A previous injury seems to make a joint more susceptible. The course of the disease is essentially chronic if untreated, but antisypilitic medication usually has a very prompt effect. It

is important to note that while these lesions may occur during any stage of syphilis, they are not common during the late periods of the disease. Pathologically but little is known of them, but they are presumed to be due to the local development of reaction to the treponema in the joint tissues. The diagnosis cannot be made from examination of the joints alone, but must be made from other signs of syphilis, either physical or laboratory.

*Synovitis*.—According to Pillón there are three types, the acute, the subacute and the chronic. The acute type may occur during any stage of syphilis, but is most frequent during the early florid manifestations. It may absolutely simulate acute rheumatic fever, for the symptoms are frequently intense, there being inflammatory swelling, pain and often high fever. The pain is severe and continuous and is aggravated upon movement. The lesions are usually localized in one or more of the large joints, but even the fingers may be affected. The swelling may be either articular or periarticular and may be very pronounced. The skin is red and may look phlegmonous. The temperature may reach 104 degrees, but there is no definite type of fever. Antisyphilitic treatment usually causes prompt disappearance. In one such case which we recently had radiographed, no local lesions could be found except a trifling periostitis about an inch above the joint.

The subacute form is simply less severe than the form just described; it may be subacute from the start, or an acute case may become subacute.

The chronic type is not so well known. This form is never associated with effusion, but is always of the "dry type." Fournier thinks that the crepitating joints of old syphilitics may be due to an old mild chronic infection. However, treatment has no effect upon the group of cases that Fournier describes.

In all of these cases the diagnosis cannot be made from physical examination of the joints alone; both thorough physical and laboratory investigation are required. It cannot be too strongly emphasized that every case of joint trouble, be it acute or chronic, should have a routine Wassermann done.

Hydrarthrosis or arthritis with effusion due to syphilis is probably not so rare as the few case reports in the literature would have us believe; it is considered unusual simply because it is not more frequently looked for. This form usually occurs before the

third year of infection. The localization is variable; sometimes it is unilateral, but it may be poly-articular and is frequently symmetrical. The joints are affected in the following order of frequency: knees, elbows, wrists and ankles. The severity of the syphilitic infection appears to have no influence upon the development of these lesions. The onset is usually insidious, and the first symptoms are usually a little discomfort and swelling. Then the swelling appears and may develop very rapidly, although various writers disagree upon this point. The skin appears normal, there is no periarticular swelling and usually there is no pain, and but little limitation of movement; there is no muscle atrophy. While there is no evidence, either clinical or radiological, of epiphysitis or of hyperostitis, pressure upon the head of the bone is almost constantly painful. Cytologic examination of the fluid fails to reveal the presence of the treponema. At the onset there are usually some polymorphonuclear leucocytes in the fluid, and later examination shows lymphocytes.

It has been suggested that cases of true intermittent hydrarthrosis, a condition which is characterized by a periodic swelling of one or of several joints without fever, may be due to syphilis. However, in one case which I saw there was absolutely nothing to substantiate the hypothesis. It should always be borne in mind that, as D'Arcy Power points out, syphilis can give an intermittent effusion into the joints, the trouble, however, persisting for some considerable time.

Osteochondroarthropathies, the pseudowhite swellings of the French authors, are in reality due to destructive or proliferative gummous changes in the vicinity of joints, and occur only during the late stages of syphilis. This disease is not especially common, Fournier reporting but 30 instances among 5000 syphilitics. The knee is affected in about 60 per cent of the cases; next in frequency rank the shoulders, elbows and wrists. Varying clinical pictures are presented according to the stage of the disease and the extent of the gummous changes. The lesions are most apt to begin either in the periosteum or at the edge of the epiphysis, and in the early stages different clinical findings would naturally result, as in the former case the swelling would be more localized at one side of the bone, whereas in the latter instance there would be a uniform

swelling. During this early period there is usually nocturnal pain, tenderness on pressure and no fever. As the swelling increases, the use of the joints is usually but little limited and the skin shows no changes. As the disease progresses, deformity may limit free movement, and if the synovial membranes become affected, effusion is prone to result. At this advanced stage the joint is globular, the overlying skin is thinned by distention, the muscles appear smaller, the limb is not held in an abnormal position; there is no ankylosis and no local adenopathy. The course of the disease may vary considerably: there may be spontaneous healing, and the resulting scar formation cause ankylosis or considerable deformity; fistulae may form and the development of sequestra prevent healing; the joint may become secondarily infected with the formation of pus.

This type of disease is extremely difficult to differentiate from tuberculosis, and unquestionably many syphilitics have been treated for tuberculous joints; at present the employment of the Wassermann reaction and of careful physical examinations for syphilis should almost invariably prevent such disastrous mistakes. The diagnosis cannot be made from local examination alone, or from the history.

The roentgen ray findings will be fully discussed in the section dealing with the value of the x-ray in diagnosis.

Gummosis perisynovitis is very rare and usually appears in from five to eight years after infection. The knee is most apt to be involved, but the elbow, wrist or ankle may be affected. The disease is usually monoarticular. The onset is insidious, there is first noticed a little swelling of the joint, often accompanied by but little pain. As the effusion increases, the joint becomes globular, the overlying skin is white with distended veins. Some filtration and often a distinct thickening of the synovial membranes can be distinguished; frequently there is a peculiar "pasteboard" rigidity. There are no functional signs. No bone changes can be detected by the x-ray. If the disease remains untreated for a long time, there may result crepitation, due to destruction of cartilage, foreign bodies due to cartilage fragments, or even infection and ankylosis. This form is comparatively easy to diagnose, since there are no bone changes.

## TABETIC ARTHROPATHY

Tabetic arthropathy, a joint affection coming on during or preceding the early stage of tabes dorsalis, was described by Charcot in 1868, and is generally known as Charcot's disease.

A tabetic arthropathy usually affects but a single joint, but may affect symmetrical joints. The knees, ankles, hips and tarsal bones are more often affected than are the joints of the upper extremity. It occurs more often in men than in women, probably because there are more male than female syphilitics.

The pathologic process seems to start with a rapid exudation of fluid into the joint, and this rapidly extends to the surrounding tissue. With this there is a disintegration of the joint tissue, capsule, ligaments, cartilage and bone. As the swelling subsides, abnormal motion, free from pain, is a most pathognomonic sign.

Another interesting feature is the lack of the muscular atrophy, or of but a limited amount of atrophy, although this is also a sign of true syphilitic arthropathies. This is doubtless due to the ability of the individual to get about without pain, the atrophy that accompanies other joint conditions is usually in direct ratio to the amount of pain on use. In other words, atrophy is due to disuse.

The x-ray findings are typical; there is a true disintegration and admixture of all the tissues, portions of bone, for instance, being found at a considerable distance from their original location. At times there appears to be a bone overgrowth, the so-called hypertrophic type; at other times there appears to be a special bone absorption, the atrophic type.

The pathologic findings are just what we should expect in a rapidly disintegrating joint; the synovial membrane is indurated with villous formation, the cartilage is thinned or frayed and there may be an ulceration or eburnation of bone.

I feel that most cases of so-called Charcot's joints are in reality syphilitic joints. In the past year I have examined x-ray plates of ten cases, diagnosed as tabetic arthropathies, and in each instance there were positive findings of luetic lesions. The hypertrophic type is undoubtedly due to the direct action of the treponema. Other syphilographers have the same feeling. Stokes, of the Mayo Clinic, agrees with me in this.

*Pseudoarthritis Deformans (of Mericamp).*—Fournier, Mericamp,



Dumesnil, Danjon and Fougquet have described cases of arthritis deformans due to syphilis. More recently O'Reilly has reported positive Wassermanns in some cases of arthritis deformans. According to the French authors it affects the large joints, especially the elbows and knees. The beginning is the deformity, for hyperostoses of the epiphyses and irregular bony outgrowths both limit movement and cause crepitation. Ordinarily treatment has no effect, but Schmidt has reported a case of hypertrophic arthritis that was cured by antisyphilitic medication. Pillon comments that these lesions resemble the deforming tuberculous rheumatism of Poncet.

#### SYPHILIS OF THE MUSCLES

Four types are mentioned, first myalgia, second frank gummata, third diffuse myositis, and last a progressive weakening of the muscular power.

Myalgia is unquestionably comparable to arthralgia and is probably due to local reactions against invading organisms. There are no objective symptoms, but subjectively there is pain, usually worse at night and aggravated by movement. Points of tenderness can usually be determined. The muscles most frequently affected are those of the thighs and legs and the deltoids, but the shoulder muscles may also be involved. Treatment usually gives a prompt response.

Gummata are probably most frequent in the muscles of the tongue but may occur in any muscles, notably the triceps and abdominal.

Diffuse myositis is rare and is due to a diffuse infiltration of the muscles by miliary gummata, and is comparable to the same condition that so frequently affects the glands of the body. No redness and usually no tenderness is apparent, but the muscles become hard and contractures develop. In one case recently shown in Washington nearly all of the muscles of the body were affected, but as a general rule the process is limited to one or two, notably the biceps and gastrocnemius, flexors of the forearm, pectoralis major, sternomastoid, masseter and abdominal muscles. When the disease is established, but little is to be expected from treatment, although much comfort may be given.

## SYPHILIS OF THE TENDONS AND TENDON SHEATHS

Syphilis of the tendon sheaths, although rare, is more frequent than in the less vascular tendons. Inflammation of the former occurs in the two forms, the serous and the gummous, while in the latter only gummata have been described.

Serous tenosynovitis usually occurs during the earlier stages of the disease and is a simple serous inflammation leading to effusion. It is most frequent in the tendon sheaths at the back of the wrist and in those of the front of the ankle, but may occur in the peronei or the hamstrings, as well as the biceps or supinator longus.

Gummous tenosynovitis occurs during the late stages in one or two forms, either diffuse or localized, and is rather more common than the type just described. Ulceration through the skin is the usual rule, but treatment usually results in a speedy cure.

## SYPHILIS OF THE BURSAE

Churchman's excellent description may be quoted: "The picture, then, is one of an indolent affection of the bursae, involving most often the knees—particularly in women. The disease is quite independent of syphilitic arthritis, the bursae involved being most often those unconnected with the joints, and the neighboring joints themselves being entirely free from involvement. In the secondary stages simple hygroma is frequent; in the tertiary stage, gummatus, ulcerating, and fungous forms occur. The bursae involved are those most exposed to trauma; but a study of the disease makes it clear that trauma, as usual in syphilis, only determines the site which the disease will occupy. There is little or no accompanying functional disability; and specific treatment leads to a prompt and permanent cure. In view of the marked indolence of the condition and its great similarity to the arthropathies of syphilis, it should be spoken of as luetic bursopathy (of Nerneuil) the possibility of the rare occurrence of more acute symptoms being, however, kept in mind."

## Section 13

## SYPHILIS OF THE GENITOURINARY ORGANS

It may be stated that in syphilis the urinary and genital organs, testicles excepted, enjoy relative immunity from infection. And

for that reason the subject has received scant attention in the current textbooks. But, as we shall see, this immunity is only relative.

#### SYPHILIS OF THE KIDNEY

Acute syphilitic nephritis occurs as an early complication following infection. This form of nephritis, while presenting certain more or less characteristic clinical symptoms is in general comparable to the nephritis following any of the acute infective diseases. In its clinical, as well as pathologic aspects, it more closely resembles postscarlatinal nephritis. In addition to this form complicating the early or secondary stage of the disease, syphilis attacks the kidney in the late or tertiary stage, and gives rise to quite different pathologic changes, more particularly interstitial changes, amyloid degeneration, and the formation of gummata. Furthermore, in congenital syphilis kidney lesions occur at two distinct periods; in early life associated with other visceral lesions and congenital stigmata, and as a late complication.

Various classifications of syphilitic lesions of the kidney have been proposed. For the purpose of clinical study the following classification will suffice.

1. Secondary stage.
  - Transient albuminuria.
  - Acute and subacute nephritis-preroseolar nephritis.
2. Tertiary stage.
  - Chronic interstitial and parenchymatous nephritis—contracted kidney (Schrumpfniere).
  - Amyloid kidney.
  - Gumma of the kidney.
3. Congenital syphilis.
  - Early nephropathies.
  - Late lesions.

#### SECONDARY STAGE

*Transient Albuminuria.*—During the period of incubation and especially associated with the appearance of the skin eruption a slight but definite albuminuria occurs. Casts are never present, and other evidences of serious damage to the kidney structure are wanting. The albumin disappears rapidly under specific treatment. This must not be confused with the acute nephritis occurring during the secondary stage.

*Acute and Subacute Nephritis.*—This form of nephritis, (nephritis acuta syphilitica precox of Hoffmann) occurs at any time after the

initial lesion. A form developing within a few weeks after the chancre and before the outbreak of cutaneous manifestation has been described.

This form of the disease may be easily overlooked, occurring as it does before the outbreak of the cutaneous rash. Its recognition is very important, however, in order that prompt treatment may be undertaken before serious damage to the kidneys has occurred. In this early stage the results of specific treatment are much more prompt and certain.

Aside from the preroseolar nephritis which is characterized by its early onset and the absence of grave constitutional symptoms, acute syphilitic nephritis occurs in association with or subsequent to the outbreak of the cutaneous lesions. This complication may develop any time during the first two years, especially during the first year after the primary sore.

The first symptom is usually edema of renal distribution. This develops rapidly and general anasarca may quickly result. Hematuria is the first symptom in some cases and may be severe. In other cases, progressive weakness with anemia and loss of weight are the symptoms first noticed.

The urinary findings resemble those found in the more common forms of acute nephritis. The amount of urine is less than normal, it is clear amber or smoky, acid in reaction, with a high specific gravity. The sediment contains a few red cells, leucocytes, epithelial cells, and hyaline and granular casts. According to Munk, lipid casts are numerous, but these are usually overlooked and classified as granular casts. The most distinctive finding is the large amount of albumin. The extraordinary grade of albuminuria which is characteristic of acute syphilitic nephritis is surpassed in no other form and is most closely approached in the postscarlatinal variety. Fifteen and twenty-five grams of albumin daily are not uncommon.

Munk has found doubly refractile lipoids in the urine of patients suffering with severe forms of nephritis. He believes there is a peculiar relation between syphilitic nephritis and the presence of these lipoids in the urine. A microscope provided with a Nicol prism is necessary for their demonstration. Under an ordinary microscope these lipoids appear as fat globules, but under polarized light they show a dark central cross separating four bright periph-

eral quadrants. According to Stengel and Austin, lipid globules have been found normally in certain tissues, for example, in the adrenal cortex, thymus, lutein cells, the puerperal uterus, mesentery, and chorioid plexus. Pathologically they have been found in arteroma, amyloid kidneys, chronic nephritis with marked cellular degeneration, in the urine of nephritis, in albuminuric retinitis, in the epithelium of the pulmonary alveoli in pneumonias and tuberculosis, in neighboring lymphatics and the septum, in the gall bladder and hepatic ducts during cholangitis, in pyogenic membranes, chronic mastitis, mesenteric tabes, actinomycesis, xanthomata, and in certain neoplasms (carcinoma, sarcoma and lymphosarcoma).

These authors report a series of twenty-three cases showing an abundance of albumin and casts in which six cases with a positive Wassermann all showed lipoids in the urine. In fourteen non-syphilitics only five showed the presence of the lipoids. And they add that with but one exception the cases which showed an abundance of the lipoids were syphilitic. It would seem, therefore, that while the presence of the globules in the urine in the case of a severe nephritis cannot be considered specific, an abundance of lipoids present in such cases is highly suggestive of syphilis.

The diagnosis is based upon the following criteria: (1) The proof of recent syphilitic infection. (2) The association of nephritic symptoms with the symptoms of recent syphilitics. (3) The absence of the other causes of nephritis. (4) The special features of the disease. (5) The urinary findings. (6) The therapeutic test.

In certain cases there may be some difficulty in differentiating between syphilitic nephritis and nephritis due to mercury. Confusion is most likely to occur in patients on mercury treatment having a marked albuminuria when they first come under observation. The importance of differentiating between a nephritis due to treatment and that due to the disease is obvious. In such cases treatment by mercury should be suspended at once and a careful note made on the behavior of the albuminuria. If due to mercury this will gradually subside. If the albumin does not entirely disappear after suspension of mercury treatment one cannot exclude syphilis as a causative factor in its production. One should then have recourse to arsphenamine given cautiously in fractional doses. As pointed out by Stokes the substitution of arsphenamine for mercury is an easily available means of establishing the syphilitic character of an

albuminuria, when previous mercurialization has confused the picture.

In any case of nephritis developing under treatment with mercury, confusion is less likely to occur. Frequent examination of the urine will detect an albuminuria before it has reached a grade where the two forms are apt to be confused. The onset of a mercurial nephritis is characterized by diuresis and cylinduria, features which readily differentiate this form from a pure syphilitic nephritis.

Arsphenamine administered with care and judgment is indispensable in the treatment of these patients.

*Treatment.*—The same general principles governing the management of other forms of acute nephritis apply to the treatment of acute syphilitic nephritis. The diet should be bland and unirritating to the kidneys. A rigid milk diet is recommended by some. Others insist that a more liberal diet, especially meats, is necessary to keep up strength and general nutrition of the patient. The general aim should be to restrict the proteins and salt, at the same time maintaining the body weight as far as possible by a liberal bland diet.

Most writers have emphasized the value of mercury in the treatment of this form of nephritis, at the same time pointing out the danger from its use. Improvement under this drug is often prompt and striking. The results are much better when the condition is recognized early and treatment promptly instituted. Karvonen goes so far as to question the diagnosis in any case not improved by mercury. On the other hand an increase in the albumin and casts has been noted following its use (Billings, Munk). But Munk has suggested that this may be due to the diuresis and the flushing out of the kidneys. Marlot states that the improvement is often slight and transient and in one-third of the early cases and in an even larger number of late cases the issue is fatal in spite of all treatment. Mercury should be given by inunctions or intramuscular injection. The dosage should be carefully guarded at first to avoid kidney irritation and the production of mercurial nephritis.

As pointed out by Marlot and emphasized by Stokes it is difficult to evaluate the usefulness of arsphenamine in the treatment of acute syphilitic nephritis on account of the small number of recorded cases. When this remedy was first introduced, renal complications

according to Ehrlich constituted a definite contraindication to its use. And the cases of hemorrhagic nephritis following its administration reported by Nanta and others served to further discourage its use. However, it was inevitable that in these desperate cases, both acute and chronic, arsphenamine would be employed; and experience has shown that in such cases it is more irritating to the kidneys than mercury; and the therapeutic results appear to be better.

#### TERTIARY STAGE

Recent authors have not only accepted syphilis as the causative factor in many cases of chronic nephritis, but insist upon the importance of differentiating this group of cases. Thus Munk states that in addition to the acute nephritis, syphilis produces a chronic indurative nephritis, nephritis interstitialis chronica fibrosa multiplex (Orth).

*Symptomatology.*—The disease develops at a late period after infection. Polyuria is not so marked as in the ordinary form. Urinary sediment is small in amount. Albuminuria is abundant and with a bipoiduria may persist for years without any associated vascular changes. Marked anemia is quite characteristic and may be associated with enlargement of the liver and pancreas. The disease occurs at a time when arteriosclerosis does not appear, from twenty-eight to thirty-seven years.

*Treatment.*—In long-standing cases with amyloid changes little or nothing can be expected from specific treatment. As Dieulafoy puts it, "waxy degeneration in old syphilitics is a tenacious and irremediable lesion." Likewise unfavorable are the cases with secondary changes in the parenchyma. In less chronic cases in which extensive degenerative changes have not yet occurred, improvement may be obtained by antisiphilitic treatment. Arsphenamine is better adapted than mercury as it is less injurious to the kidney, and more effective against the disease (Bauer). According to this same author infection in these cases is intensive and demands vigorous treatment. Arsphenamine is well borne according to Munk who recommends a dosage of 0.2 to 0.3 grams. Mercury should follow the administration of arsphenamine. This is well borne if care is used in beginning with intramuscular injection of small doses of a soluble salt and this is followed by inunctions.

*Amyloid Kidney.*—Syphilis has long been recognized as an etiologic factor in the production of amyloid or waxy degeneration from the long-continued action of toxins.

*Gumma.*—Gummata of the kidney are habitually multiple, and vary in size from a hazelnut to a walnut. More rarely the whole organ is involved in a single large gummous tumor. Gummous deposits are usually present in other organs, liver, spleen, testicles, etc. When the gummata are limited to the cortex the remainder of the kidney may appear quite normal, more often it is lobulated and scarred or enlarged and amyloid.

Seiler studied the symptoms in one case over a period of years. The diagnosis in this case was confirmed by autopsy. There was an intermittent albuminuria with blood and detritus in the urine. Subjective symptoms were absent. In large gummous tumors there may be local pain, tenderness and discomfort due to pressure.

#### PAROXYSMAL HEMOGLOBINURIA

The association of syphilis, particularly congenital syphilis with paroxysmal hemoglobinuria has long been noted. Just how frequently syphilis is associated with this disease is still undetermined.

Recent hematologic studies have shown that the plasma of hemoglobinuric patients contains a complex hemolysin of amboceptor-complement nature. At a low temperature the amboceptor combines with the red corpuscle. Subsequent elevation of the temperature causes union of the complement, and hemolysis occurs.

Hoover and Stone state as the result of their study that the lytic substance present in the blood of these patients is a biologic product of some form of infection. But as pointed out by Moss all efforts to find an infectious agent in the blood have failed. And he adds that of all suggestions so far made that of congenital syphilis seems to have the most evidence in its favor. In the two cases recorded by Moss the Wassermann test was positive.

#### SYPHILIS OF THE BLADDER

*Etiology.*—Lesions of the bladder occur during the secondary and tertiary periods of the disease. In the parasyphilitic diseases the bladder is commonly involved, notably in tabes. Age and sex have no influence upon the development of the bladder lesions. As tabes



occurs more frequently in males, however, the associated bladder disturbance is more often observed in this sex.

#### SECONDARY SYPHILIS

Nine cases of secondary syphilis of the bladder have been reported, six males and three females. The youngest was a child four years old infected by its nurse. At autopsy extensive ulcerations of the mucus membranes including bladder and urethra were found. The liver was syphilitic. In all cases bladder lesions were accompanied by secondary syphilis elsewhere, skin, mucus membranes, etc. Macules, papules, and ulcerations have been described. Durieux has described a macular eruption resembling the roseola of the skin. In Fenwick's case (postmortem) papules were disseminated over the bladder mucosa resembling condylomata. The ulcers are usually multiple, two to twelve, rounded or oval, superficial, with a slightly elevated edge and a necrotic base. They occur most frequently about the ureteral orifices, but may be found in other parts of the bladder. The adjacent mucosa is edematous, hyperemic and the vessels are injected and prominent. The remainder of the bladder appears normal.

The urine is often perfectly clear. In the presence of infection it is turbid due to the presence of pus and organisms. It may be bloody from the presence of red blood cells. The presence in the urine of the treponema has been reported, but this observation has not been confirmed.

#### TERTIARY SYPHILIS

Gummata of the bladder develop insidiously like all new growths and in the early stages produce little or no disturbance. Urination is slightly more frequent and associated with mild discomfort in the region of the bladder, in the perineum, or urethra. Hemorrhage, sudden in onset and profuse, may be the first and only symptom noted. More often symptoms of cystitis develop and increase rapidly in intensity.

Hematuria is the most constant and most striking symptom of tertiary bladder syphilis. It closely resembles the hemorrhage of new growth of the bladder. It appears suddenly without pain and is uninfluenced by rest or posture. It may continue for days, or weeks, and gradually subside only to recur after a longer or shorter

period. Complete retention may result from the formation of clots within the bladder.

*Cystoscopic Appearance.*—As viewed by the cystoscope two varieties of lesions occur, gummous ulceration and papillomatous growths. The former are more common, the latter are rare. They occur separately but may exist together.

*Treatment.*—A striking feature of bladder syphilis is its prompt response to a specific treatment.

#### THE BLADDER IN PARASYPHILITIC DISEASES

It has been known for a long time that in the course of certain diseases of the nervous system (tabes, general paralysis), which we now designate as parasyphilitic, the bladder is involved indirectly. In tabes the disturbance of the bladder function may be the first and for a long time the only evidence of a cord lesion.

The symptoms in many cases are strikingly similar to those observed in prostatic obstruction; difficulty in starting the stream, voiding in a small stream without force, frequency, intermittent flow—pumping urine out in successive efforts—marked straining on urination, incontinence of urine especially at night (bed wetting), and retention of urine, partial or complete.

The partial retention of tabes differs from that due to mechanical obstruction in one essential particular; in the latter case the amount of residual urine is constant while in tabes the amount varies from time to time within rather wide limits, from almost nothing to several hundred cubic centimeters.

In a large percentage of early cases cystoscopy shows certain characteristic changes in the bladder cavity associated with the disturbance in function. These changes in the tabetic bladder are so constant and characteristic that the diagnosis is frequently made by the urologist long before other symptoms of the cord lesion are in evidence. Examination reveals a varying amount of vesical retention without demonstrable mechanical obstruction. Cystoscopy will show the following changes: (1) Trabeculation, (2) relaxation of the vesical outlet, (3) elevation and hypertrophy of the trigone.

Trabeculation of the bladder, Balkenblase, is the most constant intravesical change associated with tabes. These trabeculae are composed of a fine interlacing network of muscle bundles and are particularly well marked at the base and on either side of the tri-

gone. They not infrequently extend high up laterally and may involve the entire bladder wall. The trigone is never involved. The texture of the trabeculation is peculiarly fine and delicate in marked contrast to the coarse trabeculae observed in prostatic obstruction.

#### SYPHILIS OF THE PROSTATE

The prostate is rarely involved in syphilis. The disease occurs most frequently between the ages of thirty and fifty years. The youngest patient was twenty-eight years old. (Reliquet.) The lesions develop during the tertiary period, years after the primary infection. This interval varies widely in the cases reported.

Rectal examination discloses a greatly enlarged, indurated prostate with an irregular, nodular surface. The enlargement is not uniform; the right lobe is most frequently involved. The induration may extend high up over the bladder wall, and the rectum may be adherent (Desnos). By reason of the hard, cartilaginous consistence and the irregular, nodular surface, the condition is usually confused with malignant disease. These changes are probably due to gum-mous deposits within the gland surrounded by dense fibrous tissue, sclerogum-mous lesions.

#### SYPHILIS OF THE SPERMATIC CORD

Syphilitic affection of the spermatic cord is rare. The cord may be involved in a diffuse funiculitis. It is then decidedly thickened, indurated, and fused with the surrounding tissues. Reclus reports two cases in which the vasa deferentia were as stiff and rigid as a glass rod and attained the size of a pen holder.

More commonly one palpates a nodular swelling along the course of the cord between the epididymis and the external ring. In size this tumor varies from an almond to a goose egg.

#### SYPHILITIC EPIDIDYMITIS

Primary syphilitic epididymitis without involvement of the testicle is rare.

The earliest appearance of epididymitis after infection is two months. It appears more frequently between one and five years. Two forms of the disease have been observed: (a) a subacute or chronic epididymitis occurring in the late secondary or early ter-

tiary stage. This is sometimes bilateral. The globus major is chiefly affected, but the process may extend to the body, tail and even into the vas. (Wright's cases.) The swelling is gradual, progressive, and for the most part painless. At first smooth and elastic, this becomes irregular, nodular and very hard or cartilaginous as the disease progresses. Effusion into the tunica vaginalis takes place forming a hydrocele which may interfere with palpation and renders the diagnosis obscure.

The course of the disease is essentially chronic. Acute development and the presence of subjective symptoms are rare. The patient's attention is often directed to the condition by the gradual increase in the size and weight of the scrotum due to the accompanying hydrocele. On palpation one feels a hard, indurated and nodular globus major with a characteristic sharp edge which caps the testicle like a helmet. Less frequently the process extends to the body and tail of the epididymis. A distinct sulcus separates the enlarged epididymis from the testicle. There is little or no sensitiveness on pressure. The testicle is not involved and the vas is normal.

(b) Small gummata may occur in the epididymis in the tertiary stage. They appear as hard, indurated nodules, confined to the epididymis. When the whole organ is involved gummatous deposits will often be found along the cord of the same side. These show little tendency to break down. This condition resembles tuberculous infection with which it is easily confused.

#### SYPHILITIC ORCHITIS

Two forms of the affection are recognized: a diffuse interstitial sclerosis which is the most common form, and gumma of the testicle. The two forms are rarely distinct.

Gumma of the testicle is much less common than is generally supposed. In the series of autopsy cases reported by Symmers not a single case of gumma of the testicle was encountered. The same experience is reported by other pathologists. Gummata usually develop in a testicle already the seat of a diffuse or partial interstitial orchitis. The affection is characterized by the development of one or more small, hard, or elastic nodules which gradually increase in size. These nodules are surrounded by a dense fibrous capsule by which they are sharply defined from the surrounding

tissue. A large gumma may break down, become adherent to the overlying skin, break through and discharge necrotic material. A deep ulcer with a sloughing necrotic base results.

Syphilis of the testicle must be differentiated from tuberculous disease, gonorrheal epididymitis, hematocoele and new growth.

In tuberculous disease the primary focus is in the epididymis chiefly the globus major, which is enlarged, infiltrated, and nodular. The vas is often thickened and nodular. The overlying skin becomes adherent and fistulization occurs relatively early with the discharge of the characteristic thin tuberculous material. In such cases we can always trace the fistulous tract directly to the epididymis while in syphilis the fistulous tracts extend to and communicate with the testicle proper. In tuberculous infection associated lesions of the prostate, seminal vesicles, or bladder may be in evidence. The subjective symptoms and local signs are always more marked.

There should be no difficulty in differentiating gonorrheal epididymitis. Confusion arises only in the exceptional cases of acute syphilitic orchitis. And here a careful history together with the absence of other evidence of urethral infection will lead to a correct diagnosis.

The greatest difficulty is experienced in differentiating cases of syphilis and tumor of the testicle. It may be quite impossible to differentiate these two conditions by the local examination alone.

*Prognosis.*—The prognosis in general is good. Atrophy results from the excessive development and contraction of connective tissue in neglected cases. But where the glandular structure has not been destroyed this will continue to functionate when the process has been arrested by appropriate treatment.

*Treatment.*—As syphilis of the testicle responds promptly to anti-luetic treatment this should be pushed vigorously. The patient should be warned that the affected testicle may be smaller than normal following treatment and that the longer treatment is delayed the greater the chances of losing completely the function.

## SYPHILIS OF THE FEMALE GENITAL ORGANS

### LESIONS OF THE VULVA

Chancre of the vulva has already been described, but perhaps it would not be amiss to again call attention to the fact that a con-

siderable amount of edema frequently accompanies a chancre upon one of the labia majora. Of the secondary lesions condylomata are much the most frequent, and practically the whole surface of the labia may be converted into condylomatous masses, which at times assume a hypertrophic aspect. Ravogli has called attention to frequency of true venereal warts, due to the irritating discharge from syphilitic lesions.

#### LESIONS OF THE VAGINA

Because of the resistance of the mucous membrane of the vagina, and also because of the character of the secretions, chancre of the vagina is exceedingly rare.

Secondary lesions of the vagina are very rare. Late lesions but rarely originate in the vagina.

#### LESIONS OF THE CERVIX

The frequency of initial lesions upon the cervix is given by various observers as from 1 to 15 per cent of all chancres occurring in women. Women who have borne children are apt to develop cervical chancres, probably because of lacerations and erosions. The anterior lip is rather more often affected than is the posterior, and multiplicity is not uncommon.

Secondary lesions are probably more common than the rather scanty literature would seem to indicate.

#### LESIONS OF THE UTERINE BODY

Several cases of gummata of the muscular body have been described, in the latest by Norris, who states that there are two types of gummata, one where there is a diffuse infiltration and the second where there is one localized lesion.

#### LESIONS OF THE OVARIES

Simple enlargement, syphilitic oophoritis, tertiary sclerosis, and true gummous formation have been described, but the authors have furnished but little real proof of these lesions being of a syphilitic nature according to Gellhorn and Ehrenfest.

#### LESIONS OF THE BREAST

During the early eruptive period there may occur an acute mastitis, with diffuse swelling and pain; this may be either unilateral

or bilateral. It is analogous to the swelling that may occur in the thyroid or the salivary glands at the same period.

Sauvages was probably the first to recognize the late manifestations of mammary syphilis. Probably the commonest form is the localized gumma, examples of which have been described by Power, Bryant, Sheild and others. Usually the lump breaks down rather rapidly, and this point will serve to exclude cancer. Also neighboring glands but rarely become enlarged, which by the way, is not a point of any great value in differential diagnosis. It may be very difficult to exclude chronic mastitis or tuberculosis except by laboratory tests, or the findings of other signs of lues.

The second form of mammary syphilis is the rare, diffuse syphilitic infiltration, which is due to miliary gummata, and which is analogous to the condition occurring in so many of the internal glandular organs. Ambrosoli has reported two cases.

## Section 14

### AFFECTIONS OF THE ENDOCRINE GLANDS

As the work upon the vegetative neurology increases, it becomes evident that the activities of the ductless glands are closely associated with the action of the vagus and sympathetic nerves. It is probable that in the future it will be found that endocrinology will be recognized as but a branch of vegetative neurology.

#### SYPHILIS OF THE THYROID GLAND

There are two different types of hypersecretion, the sympathicotonic and the vagotonic. In the former there is well-marked exophthalmos, marked tachycardia, dry skin, falling hair and alimentary glycosuria, while in the latter there is no exophthalmos, but slight tachycardia, and marked palpitation, sweats, hyperacidity of the stomach, diarrhea, and unlesened carbohydrate tolerance. The two groups also show very different eye signs, for in the former, there is a negative von Graefe (dissociation between the movements of the upper lid and of the eyeball), positive Loewi (epinephrine mydriasis) and a positive Noebius (insufficiency of convergence), while in the latter the von Graefe is positive and the Moebius negative.

There is but little literature as to the hyperthyroidism caused

by syphilis, but it undoubtedly can occur in early syphilis, for we all know that infections may cause a temporary oversecretion. One would naturally think that gummous formation where there is a destruction of tissue would cause undersecretion, but this was not always the case. It would seem that perhaps syphilitic changes in one portion of the gland may stimulate the remainder to over-secretion.

In conditions of hypothyroidism the gland can usually not be felt, the skin is thickened and dry, there may be supraclavicular fat pads, the face lacks expression, all of the metabolic processes are slowed, the temperature is frequently subnormal, constipation is the rule, and there is evident lack of memory and slowness of thought.

There is very little literature as to the part that syphilis can play in causing hypothyroidism, however, one cannot help feeling that if an interstitial thyroiditis exists, as occurs in practically all other organs, there should be some symptoms. As bearing upon this point Kohler has reported a case where a woman of forty-eight had a tumor of the thyroid that disappeared under iodides; a concomitant myxedema also disappeared. Pospelow has also reported an instance where myxedema developing in an undoubted syphilitic was cured by antisypilitic medication. More observations upon this point are much needed.

However, the literature does deal with three distinct types of lesions, the diffuse swelling of the gland associated with early syphilis, gumma formation, and disturbances caused by administration of iodine.

In 1906 Mendel suggested that some of the so-called cases of thyroid syphilis might be merely examples of iodine thyroiditis. He felt that most of the early cases were of this nature. This view has escaped the general attention that it deserves, in spite of the fact that symptoms of hyperthyroidism may be caused by large doses of the iodides.

#### SYPHILIS OF THE PARATHYROIDS

I can find no references concerning syphilitic lesions of the parathyroids, and yet it is reasonable to infer that some of the above-mentioned phenomena might be due to luetic lesions.



## SYPHILIS OF THE THYMUS

The literature contains a number of references to congenital syphilis of the thymus, but there are no cases of acquired lues of this gland upon record.

## SYPHILIS OF THE PINEAL GLAND

Concerning syphilis of the gland we are totally ignorant.

## SYPHILIS OF THE SUPRARENALS

Irritative lesions of the medulla of the adrenals, causing over-secretion result in rapid pulse, increase in blood sugar, increased blood pressure, shortened coagulation time, and irritability of the vasomotor system. Destructive lesions of the medulla naturally cause an opposite set of symptoms, namely, cyanosis, and sometimes heart failure. At this point it is interesting to note that it has been experimentally shown that arsenic and arsenic compounds may have a destructive action upon the medulla.

Irritative lesions of the cortex produce the syndrome of suprarenal virilism, while destructive lesions produce Addison's disease, with its low blood pressure, weakness and pigmentation.

Pathologists now recognize that syphilis of the adrenals, in the form of areas of round-celled infiltration, is very frequently found in autopsies upon patients dying of syphilis. Warthin is very emphatic upon this point.

But little is known of secondary syphilis in the adrenals. Various men have attributed the asthenia, sometimes seen at this stage of the infection, to changes in the adrenals, and Giuranna has described changes in the cells, a finding that Sezany was unable to confirm in autopsy upon three cases. However, in the late stages of syphilis a few cases of Addison's disease have been reported, one by Thompson and another by Schaffner and Howard. Addison's disease due to syphilis is probably commoner than has been believed.

## SYPHILIS OF THE PITUITARY

A considerable number of cases of gumma of the pituitary have been described, most of them in women, curiously enough. In many of the cases there was no clinical history, the patient having died

soon after admission to the hospital, or the lesions having been found at autopsy. The symptoms to be expected would naturally be those of increased internal pressure, local symptoms due to local pressure, and those due to lack of function.

In the cases reported by Stroebe and Turner the disease was very acute, death resulting in six weeks. Semicomatose attacks seem to be the outstanding feature. Other observers have reported polyuria, tremors, and amenorrhea.

# STUDIES IN THE STANDARDIZATION OF THE WASSERMANN REACTION, XXVII\*

## A STUDY OF FACTORS INFLUENCING THE TITRATION OF ANTIGEN

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(Received for publication November 30, 1920)

OF course it is well known that tissue extracts employed as antigens in complement-fixation tests for syphilis may vary considerably in their properties and that one of the most important factors influencing the reaction is the *amount* as well as the kind of antigen employed.

A decision regarding the fitness of an extract and the amount to employ, rests upon the results of titrations for anticomplementary, hemolytic and antigenic activities; at the present time the methods employed for these titrations vary considerably and the object of our investigation was to study the factors influencing these titrations so that a uniform method may be proposed as an important step toward standardization of complement-fixation technic.

### Part 1.

#### FACTORS INFLUENCING THE ANTICOMPLEMENTARY TITRATION

*The Influence of Primary Incubation.*—Some serologists do not incubate the antigen-complement mixtures before adding hemolysin and corpuscles to determine the degree of complement absorption or destruction; others incubate a variable period not at all similar to the primary incubation employed in their complement-fixation tests and others use one-half or one hour in a water bath or air incubator and conduct the main complement-fixation tests with a primary incubation in a refrigerator. These practices introduce error; *in conducting this titration the antigen-complement mixtures should receive exactly the same primary incubation as employed in the*

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\*Investigation aided by funds accruing from the preparation of arsphenamine.

*complement-fixation tests.* Previous studies<sup>1, 2, 3</sup> have shown the profound influence of temperature and duration of primary incubation upon specific and nonspecific complement fixation and the subject requires but brief mention in relation to the titration of antigen.

As shown in Table I the kind of primary incubation exerts considerable influence upon the results of anticomplementary activity; an antigen was free of anticomplementary effects in 1.0 c.c. of 1:10 dilution when hemolysin and cells were added at once but with a primary incubation of one hour in a water bath the unit was 0.6 c.c. and with eighteen hours in a refrigerator at 8 C. the unit was 0.2 c.c. Further examples of a similar kind are shown in Table II, indicating the important relation of primary incubation to anticomplementary titration and especially that antigens are more anticomplementary after refrigerator incubation than one hour in a water bath or air incubator. For this reason a complement-fixation technic based upon water bath incubation may not be adapted for the refrigerator method; *certainly a dose of antigen based upon water bath incubation may be too large for complement-fixation tests conducted with a primary incubation in a refrigerator for eighteen hours.*

TABLE I  
THE SPEED OF ANTICOMPLEMENTARY ACTIVITY OF ANTIGENS

PRIMARY INCUBATION	ANTICOMPLEMENTARY UNITS		
	ANTIGEN I*	ANTIGEN II	ANTIGEN III
No primary incubation	—**	—	—
15 minutes in water bath	—	—	—
30 minutes in water bath	—	0.7 c. c.	—
1 hour in water bath	1.0 c. c.	0.6 c. c.	1.0 c. c.
1 hour in refrigerator	—	0.9 c. c.	—
4 hours in refrigerator	0.7 c. c.	0.5 c. c.	0.8 c. c.
18 hours in refrigerator	0.4 c. c.	0.2 c. c.	0.7 c. c.

*The Influence of Method of Diluting Alcoholic Extracts with Saline Solution.*—Sachs and Roudini,<sup>4</sup> Browning and McKenzie<sup>5</sup> and others claim that antigens *slowly* diluted with saline solution are more turbid and antigenic than opalescent emulsions prepared by mixing antigen and saline rapidly; less has been written on the influence exerted upon anticomplementary effects. Bronfenbrenner

\*Antigen I—cholest. and lecithin. alc. ext. beef heart; II—cholest. alc. ext. beef heart; III—acetone insoluble lipoids of beef heart.

\*\*Not anticomplementary in 1.0 c.c. of 1:10, the largest amount used in the titration.

TABLE II

THE INFLUENCE OF INCUBATION IN A WATER-BATH VERSUS REFRIGERATOR UPON THE RESULTS OF ANTIGEN TITRATIONS

EXTRACTS	HEMOLYTIC UNITS		ANTICOMPL. UNITS		ANTIGENIC UNITS	
	WATER BATH	REFRIG.	WATER BATH	REFRIG.	WATER BATH	REFRIG.
Plain alc. extract beef heart	0.2(1:5)	0.5(1:5)	1.0(1:10)	0.9(1:10)	0.1(1:50)	0.1(1:200)
Plain alc. extract human heart	0.5(1:5)	0.8(1:5)	0.3(1:10)	0.4(1:10)	0.1(1:25)	0:1(1:100)
Cholest. alc. extract beef heart	0.4(1:5)	0.7(1:5)	0.8(1:10)	0.4(1:10)	0.1(1:50)	0:1(1:100)
Cholest. alc. extract human heart	0.2(1:5)	0.8(1:5)	0.4(1:10)	0.3(1:10)	0.1(1:200)	0.1(1:300)
Alcoholic extract syphilitic liver	0.5(1:5)	0.6(1:5)	0.9(1:10)	0.3(1:10)	0.1(1:25)	0.1(1:50)
Acetone insoluble lipoids (No. 1)	0.5(1:5)	0.8(1:5)	1.0(1:10)	0.9(1:10)	0.1(1:50)	0.1(1:100)
Acetone insoluble lipoids (No. 2)	0.5(1:5)	0.8(1:5)	1.0(1:10)	0.6(1:10)	0.1(1:50)	0.1(1:400)
Cholest. and lecithin. ext. beef heart (No. 1)	0.5(1:5)	0.7(1:5)	1.0(1:10)	1.0(1:10)	0.1(1:100)	0.1(1:300)
Cholest. and lecithin. ext. beef heart (No. 2)	0.4(1:5)	0.7(1:5)	0.8(1:10)	0.7(1:10)	0.1(1:50)	0.1(1:600)

TABLE III

THE INFLUENCE UPON ANTICOMPLEMENTARY ACTIVITY OF MANNER OF DILUTING  
TISSUE EXTRACTS WITH SALINE SOLUTION; PRIMARY INCUBATION  
18 HOURS AT 8° C.

METHOD OF DILUTING	ANTICOMPLEMENTARY UNITS 1:10		
	ANTIGEN I*	ANTIGEN II	ANTIGEN III
Saline added drop by drop	0.3	0.4	0.6
Saline added very rapidly	0.9	0.6	0.8
Extract added drop by drop	0.6	0.4	0.8
Extract added very rapidly	0.7	0.4	1.0

\*Antigen I—cholest. and lecithin, alc. ext. beef heart; II—cholest. alc. ext. beef heart; III—acetone insoluble lipoids of beef heart.

TABLE IV

THE ANTICOMPLEMENTARY UNITS OF VARIOUS EXTRACTS DILUTED 1:10 WITH  
SALINE SOLUTION; IN FOUR METHODS AND TITRATED WITH A PRIMARY  
INCUBATION OF 18 HOURS AT 8° C.

EXTRACTS	METHODS OF PREPARING EMULSIONS			
	SALINE ADDED SLOWLY	SALINE ADDED RAPIDLY	EXTRACT ADDED SLOWLY	EXTRACT ADDED RAPIDLY
No. 1 Plain alc. ext. human heart	0.4	0.5	0.4	0.5
No. 2 Plain alc. ext. beef heart	0.5	0.6	0.5	0.7
No. 3 Cholest. alc. ext. human heart	0.2	0.4	0.5	0.5
No. 4 Cholest. alc. ext. beef heart	0.2	0.6	0.5	0.6
No. 5 Acetone insoluble lipoids	0.7	0.8	0.7	0.9
No. 6 Cholest. and lecithin, ext. beef heart	0.7	0.8	0.7	0.9

and Schlesinger<sup>6</sup> found that opaque emulsions of acetone insoluble lipoids are more anticomplementary and the fluorescent are more antigenic; Ruediger<sup>7</sup> has also found that the degree of turbidity and dilution of alcoholic extracts greatly influences the results of titrations and that for each antigen there appears to be an optimum turbidity and dilution.

In conducting our experiments four emulsions were prepared of each antigen as follows:

1. Saline was added to each extract at the rate of 1 c.c. per minute; these emulsions were very opaque or turbid.

2. Saline was added to each extract very rapidly by blowing from a 5 or 10 c.c. pipette; these emulsions were opalescent.

3. Extract was added to saline drop by drop from a 1 c.c. pipette; these emulsions were opaque.

4. Extract was added to saline very rapidly by blowing from a 1 c.c. pipette; these emulsions were opalescent.

The results of titrations of these four emulsions of each of three antigens conducted at the same time with a primary incubation of eighteen hours at 8° C. are shown in Table III; a summary of similar titrations of six other extracts are shown in Table IV. Table V gives a summary of similar titrations of eight extracts with a primary incubation of one hour in a water bath.

The results may be summarized as follows:

1. The differences in anticomplementary activity of emulsions of the extracts prepared by the four methods were usually slight but occasionally quite pronounced and especially with cholesterolized extracts.

2. In the majority of titrations the turbid or opaque emulsions prepared by adding saline very slowly to the extract or the extract very slowly to the saline were more anticomplementary than the opalescent emulsions prepared by adding saline or extract rapidly.

TABLE V

THE ANTICOMPLEMENTARY UNITS OF VARIOUS EXTRACTS DILUTED 1:10 WITH SALINE SOLUTION IN FOUR METHODS AND TITRATED WITH A PRIMARY INCUBATION OF ONE HOUR AT 37° C.

EXTRACTS	METHODS OF PREPARING EMULSIONS			
	SALINE ADDED SLOWLY	SALINE ADDED RAPIDLY	EXTRACT ADDED SLOWLY	EXTRACT ADDED RAPIDLY
No. 1 Plain alc. ext. beef heart	0.4	0.5	0.4	0.6
No. 2 Plain alc. ext. human heart	0.2	0.3	0.2	0.4
No. 3. Cholest. alc. ext. beef heart	0.2	0.7	0.8	1.0
No. 4 Cholest alc. ext. human heart	0.3	0.3	0.3	0.3
No. 5 Acetone insoluble lipoids	0.6	0.8	0.7	0.9
No. 6. Acetone insoluble lipoids	0.6	0.6	—	—
No. 7 Cholest. and lecithin. ext. beef heart	0.7	0.7	0.8	0.8
No. 8 Cholest. and lecithin. ext. beef heart	0.7	0.6	—	—

3. Opalescent emulsions prepared by adding the saline rapidly to the extract were somewhat more anticomplementary than emulsions prepared by adding the extract rapidly to the saline.

4. Turbid or opaque emulsions prepared by adding the saline slowly to the extract were generally of the same anticomplementary activity as emulsions prepared by adding the extract slowly to the saline.

*From the standpoint of anticomplementary activity therefore, opalescent emulsions are preferable to opaque or turbid emulsions and especially opalescent emulsions prepared by adding the extract to the saline solution; however, the question of influence upon antigenic activity must be considered before a decision is reached regarding the best technic for diluting alcoholic extracts for complement-fixation tests.*

*The Influence of Normal Serum.*—Probably the majority of serologists omit serum in titrations for the anticomplementary activity of antigens. The presence of nonsyphilitic serum however, usually has an influence upon the results when an antish sheep hemolytic system is employed, due to the presence of natural hemolysins. As shown in Table VI when antigens are titrated in the presence of 0.1 c.c. heated nonsyphilitic serum the units of anticomplementary activity are usually slightly less than when the antigens are titrated without the addition of serum. When the titrations are conducted with serum heated for fifteen minutes followed by removal of hemolysins by absorption with sheep corpuscles and reheated for fifteen minutes to remove anticomplementary activity, the antigens were more anticomplementary than when titrated plain or in the presence of unabsorbed serum; these results were probably due to a slight anticomplementary activity of the serum, although the serum controls showed complete hemolysis.

TABLE VI

THE INFLUENCE OF NORMAL SERUM UPON THE ANTICOMPLEMENTARY TITRATION OF EXTRACTS

EXTRACTS	ANTICOMPLEMENTARY UNITS TITRATION WITH		
	PLAIN SERUM	HEMOLYSIN-FREE SERUM	NO SERUM
Plain alc. ext. beef heart	0.8(1:10)	0.4(1:10)	0.8(1:10)
Cholest. alc. ext. beef heart	0.8(1:10)	0.2(1:10)	0.7(1:10)
Acetone insoluble lipoids	0.7(1:10)	0.4(1:10)	0.5(1:10)
Cholest. and lecithin. ext. beef heart	1.0(1:10)	0.6(1:10)	0.9(1:10)

By reason of the influence of natural hemolysins and possibly of anticomplementary activity of serum upon the results of antigen titrations, the amount of serum to employ becomes a matter of practical importance; Table VII is an example of the slight variation in results due to the amount of serum employed. In our quantitative



complement-fixation tests each serum is tested in five amounts ranging from 0.1 to 0.00125 c.c.; experience has shown that titrations of antigens conducted with 0.05 c.c. of a *mixture of fresh nonsyphilitic sera heated at 55° C. for fifteen minutes* yield uniform and satisfactory results.

TABLE VII

THE INFLUENCE OF NORMAL SERUM UPON THE ANTICOMPLEMENTARY TITRATION OF EXTRACT (ANTIGEN)

SERUM	AMOUNTS OF ANTIGEN 1:10									
	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0	1.5
0.1 c. c.	-	-	-	-	-	-	+	+	++	++
0.05 c. c.	-	-	-	-	-	+	+	++	++	++
0.02 c. c.	-	-	-	-	-	+	+	++	++	++
None	-	-	-	-	-	+	+	+	-	-

*Theoretically serum should always be used in the anticomplementary titrations of antigens although practically this does not appear absolutely necessary; if serum is used it must be perfectly fresh, heated in the same manner as are the sera for complement-fixation tests, used in an averaged amount and preferably as mixed sera to approach in some degree the average in content of natural hemolysin.*

*The Influence of Heating Antigens.*—A few serologists are of the opinion that heating saline emulsions of antigens in a water bath at 55° C. for one-half hour or more, results in a reduction of anticomplementary activity; this may be true to a slight degree with emulsions kept over from day to day and contaminated with bacteria, but with freshly prepared emulsions our experiments have been uniformly negative. As shown in Table VIII which gives the results of titrations of 1:10 emulsions of four different extracts, heating saline emulsions at 56° C. for thirty minutes has no effect upon anticomplementary activity.

After boiling undiluted extracts for one hour with reflex conden-

TABLE VIII

THE INFLUENCE OF HEATING EXTRACTS AT 56° C. FOR THIRTY MINUTES UPON ANTICOMPLEMENTARY ACTIVITY

EXTRACTS	UNHEATED	HEATED
Plain alc. ext. beef heart	0.7(1:10)	0.6(1:10)
Cholest. alc. ext. beef heart	0.7(1:10)	0.7(1:10)
Acetone insoluble lipoids	0.6(1:10)	0.6(1:10)
Cholest. and lecithin. ext. beef heart	0.6(1:10)	0.6(1:10)

TABLE IX  
THE INFLUENCE OF BOILING EXTRACTS FOR ONE HOUR UPON HEMOLYTIC, ANTICOMPLEMENTARY AND ANTIGENIC ACTIVITIES

EXTRACTS	HEMOLYTIC		ANTICOMPLEMENTARY		ANTIGENIC	
	BEFORE BOILING	AFTER BOILING	BEFORE BOILING	AFTER BOILING	BEFORE BOILING	AFTER BOILING
Plain Alc. extract beef heart	0.5(1:5)	0.4(1:5)	0.7(1:10)	0.8(1:10)	0.1(1:200)	0.1(1:100)
Cholest. alc. extract beef heart	0.9(1:5)	0.8(1:5)	0.7(1:10)	0.8(1:10)	0.1(1:200)	0.1(1:50)
Alcoholic extract syphilitic liver	0.6(1:5)	0.6(1:5)	0.7(1:10)	0.8(1:10)	0.1(1:25)	0.1(1:50)
Acetone insoluble lipoids	0.9(1:5)	0.7(1:5)	0.7(1:10)	0.9(1:10)	0.1(1:100)	0.1(1:100)
Cholest. and lecithin. extract beef heart	0.7(1:5)	0.6(1:5)	0.4(1:10)	0.4(1:10)	0.1(1:200)	0.1(1:200)

sers, the anticomplementary activities appeared to be very slightly reduced with some extracts, as shown in Table IX; *the influence of heat upon the anticomplementary activities of alcoholic tissue extracts is so slight however, as to be negligible.*

*The Influence of Filtration.*—Filtration of saline emulsions through chemically clean and sterile Kitasato earthen candles completely removes the anticomplementary substances as shown in Table X; this would be an ideal method for removing these substances and those producing hemolysis, were it not for the fact that the antigenic substances are totally removed at the same time.

TABLE X

THE INFLUENCE OF FILTRATION OF 1:5 DILUTIONS OF EXTRACTS UPON  
ANTICOMPLEMENTARY ACTIVITY

EXTRACTS	BEFORE FILTRATION	AFTER FILTRATION
	1:10	1:10
Plain alc. ext. beef heart	0.3	—*
Cholest. alc. ext. beef heart	0.5	—
Acetone insolble lipoids	0.5	—
Cholest. and lecithin. ext. beef heart	0.8	—

\*Not anticomplementary in 1 c.c. of 1:10, the largest amount tested.

*The Unit of Anticomplementary Activity.*—Some serologists accept the smallest amount of antigen producing slight inhibition of hemolysis as the unit; others take the smallest amount producing complete inhibition as the unit. Frequently there is a marked difference between these two amounts as shown in Table XI, which influences the amount of antigen used when one-half to one-sixth the anticomplementary unit is taken as the dose for complement-fixation tests.

With the majority of antigens the anticomplementary units is better read as the smallest amount producing complete inhibition of hemolysis, *but antigens are occasionally encountered and especially plain or crude alcoholic extracts, which begin to produce hemolysis before this point is reached.* The plain alcoholic extract of beef heart shown in Table XI was an extract of this character; a unit based upon complete inhibition of hemolysis by this extract was not observed because of the hemolytic effects in the larger amounts. For this reason we believe *the unit of anticomplementary activity should be the smallest amount just producing beginning inhibition of hemolysis.*

TABLE XI  
THE INFLUENCE OF METHOD OF INTERPRETING THE ANTICOMPLEMENTARY UNITS OF ANTIGEN

ANTIGENS	ANTICOMPLEMENTARY TITRATIONS 1:10										UNIT ACCORDING TO SLIGHT INHIBITION	UNIT ACCORDING TO COMPLETE INHIBITION
	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0		
Plain alc. extract beef heart	C*	C	C	C	M	M	M	S	S	S	0.4	not obtainable
Cholest. alc. extract beef heart	C	C	M	S	S	S	S	N	N	N	0.3	0.8
Alcoholic extract syphilitic liver	C	C	C	C	M	S	N	N	N	N	0.5	0.7
Acetone insoluble lipoids	C	C	C	S	S	S	S	N	N	N	0.4	0.8
Cholest. and lecithin. extract beef heart	C	C	C	C	M	M	M	N	N	N	0.5	0.8

\*C—complete hemolysis; M—marked hemolysis; S—slight hemolysis; N—no hemolysis.

## Part 2

## FACTORS INFLUENCING THE HEMOLYTIC TITRATION

*The Influence of Incubation.*—As shown in Tables II and XII heat greatly favors the hemolytic activity of tissue extracts; all extracts employed in this study were more hemolytic at 37° C. in a water bath for one hour than in a refrigerator at 8°C. for eighteen hours.

Since the secondary incubation in complement-fixation tests is conducted in a water bath at 37° C. the hemolytic activity of extracts should be determined by titration at this temperature with an exposure of one hour.

TABLE XII

THE INFLUENCE OF INCUBATION UPON THE HEMOLYTIC ACTIVITY OF ANTIGEN

EXTRACTS	HEMOLYTIC UNITS 1:5		
	WATER BATH 1 HOUR	REFRIGERATOR 18 HOURS	REFRIGERATOR 18 HOURS WATER BATH 1 HOUR
Plain alc. ext. beef heart	0.3	0.7	0.2
Cholest. alc. ext. beef heart	0.5	1.0	0.8
Acetone insoluble lipoids	1.0	Not in 1.0	0.9
Cholest. and lecithin. ext. beef heart	0.5	0.9	0.4

As shown in Table II plain or crude alcoholic extracts were usually most hemolytic; the addition of cholesterol usually reduced hemolytic activity due probably to the antihemolytic activity of this substance. Acetone insoluble lipoids and cholesterolized lecithinized alcoholic extracts of beef heart<sup>s</sup> proved least hemolytic.

*The Influence of Method of Diluting Alcoholic Extracts with Saline Solution.*—The manner of diluting alcoholic extracts with saline solution does not appear to influence hemolytic activity; as shown in Table XIII four different emulsions of each of three extracts showed similar hemolytic activities.

*The Influence of Serum.*—Most serologists titrate the hemolytic activity of an extract by placing increasing amounts of an emulsion in test tubes with the corpuscles followed by incubation; as shown in Table XIV, however, *the presence of serum greatly reduces hemolytic activity and should always be used in the titrations in order to test the extract under the same conditions as it is used in complement-fixation tests.*

TABLE XIII

THE INFLUENCE UPON HEMOLYTIC ACTIVITY OF MANNER OF DILUTING TISSUE EXTRACTS WITH SALINE SOLUTION; PRIMARY INCUBATION 18 HOURS AT 8° C.

METHOD OF DILUTING	HEMOLYTIC UNITS 1:5		
	ANTIGEN I*	ANTIGEN II	ANTIGEN III
Saline added drop by drop	0.9	0.9	0.8
Saline added very rapidly	0.9	0.9	1.0
Extract added drop by drop	0.7	0.9	1.0
Extract added very rapidly	0.8	0.8	0.9

\*Antigen I—cholest. and lecithin. alc. ext. beef heart; II—cholest. alc. ext. beef heart; III—acetone insoluble lipoids of beef heart.

The results shown in Table XIV were observed with a plain alcoholic extract of beef heart; this extract began to produce hemolysis of sheep corpuscles in 0.3 c.c. of a 1:5 dilution. When 0.1 c.c. of fresh heated human serum was added to each tube the unit was greater than 1 c.c. Heated guinea pig serum complement also reduced hemolytic activity; unheated complement favored hemolysis, due to the presence of natural antisheep hemolysin.

Therefore *in the titration of extracts for hemolytic activity serum should always be included*; this serum should be heated to destroy complement. Either guinea pig or human serum (syphilitic or non-syphilitic may be employed, we use 0.05 c.c. of heated human serum.

*The Influence of Heat.*—Heating saline emulsions of alcoholic extracts in a water bath at 55° C. for half an hour appeared to slightly reduce hemolytic activities as shown in Table XV; likewise boiling the alcoholic extracts for one hour with reflux condenser appeared to reduce the hemolytic activity of some extracts to a slight extent (Table IX).

The influence of heat is, however, so slight that the procedure is not of practical value.

*The Influence of Filtration.*—As previously stated, filtration of saline emulsions of various extracts, through chemically clean and sterile Kitasato filters completely removes the hemolytic substances as shown in Table XVI; however, this procedure also removes the antigenic substances and is worthless as a practical procedure unless further studies show that the use of filters of varying density results in the removal of hemolytic and anticomplementary substances and not of antigenic substances.

*The Hemolytic Unit.*—Some serologists designate the hemolytic unit as the smallest amount of extract producing slight hemolysis;

TABLE XIV  
THE INFLUENCE OF SERUM UPON THE HEMOLYTIC TITRATION OF EXTRACT (ANTIGEN)

SERUM	AMOUNTS OF ANTIGEN 1:5									
	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0
No serum	N*	N	S	M	M	O	C	O	O	O
0.3 c.c. of 1:30 unheated complement	N	N	N	N	N	S	M	O	O	O
0.3 c.c. of 1:30 complement (heated)	N	N	N	N	N	N	S	M	O	O
0.1 c.c. human serum (heated)	N	N	N	N	N	N	N	N	N	N
0.3 c.c. 1:30 unheated complement +										
0.1 c.c. human serum	S	M	M	M	O	O	O	O	O	O
0.3 c.c. 1:30 heated complement +										
0.1 c.c. human serum	N	N	N	N	N	N	N	N	N	N

\*N—no hemolysis; S—slight hemolysis; M—marked hemolysis; C—complete hemolysis.

TABLE XV

THE INFLUENCE OF HEATING EXTRACTS AT 56° C. FOR THIRTY MINUTES UPON  
HEMOLYTIC ACTIVITY

EXTRACTS	UNHEATED	HEATED
Plain alc. ext. beef heart	0.2(1:5)	0.2(1:5)
Cholest. alc. ext. beef heart	0.9(1:5)	1.0(1:5)
Acetone insoluble lipoids	0.8(1:5)	0.9(1:5)
Cholest. and lecithin. ext. beef heart.	0.4(1:5)	0.5(1:5)

TABLE XVI

THE INFLUENCE OF FILTRATION OF 1:5 DILUTIONS OF EXTRACTS UPON  
HEMOLYTIC ACTIVITY

EXTRACTS	BEFORE FILTRATION 1:5	AFTER FILTRATION 1:5
Plain alc. ext. beef heart	0.1	—
Cholest. alc. ext. beef heart	0.6	—
Acetone insoluble lipoids	0.5	—
Cholest. and lecithin. ext. beef heart	0.4	—

\*Not hemolytic in 1 c.c. of 1:5, the largest amount tested.

others as the smallest amount producing complete hemolysis. The difference between these amounts is slight with some extracts and marked with others; in fact, with extracts of acetone insoluble lipoids a unit based upon complete hemolysis may not be obtainable at all. For this reason we believe *the unit should be designated as the smallest amount of extract producing beginning hemolysis.*

### Part 3

#### FACTORS INFLUENCING ANTIGENIC TITRATIONS

*The Influence of Primary Incubation.*—This subject has been considered in previous articles<sup>8, 9</sup> showing the great influence upon fixation of complement by syphilis antibody and tissue extracts of temperature and duration of primary incubation. With undiluted serum containing large amounts of antibody, fixation is a rapid phenomenon and may occur in a few minutes at room temperature, but with sera containing smaller amounts of antibody and with dilutions of sera, longer periods of time are required for maximum fixation.

The stronger reactions observed after a primary incubation of antigen, antibody and complement at 8° C. for eighteen hours as compared with one hour at 37° C. have been ascribed to a greater



deterioration of complement,<sup>1</sup> greater nonspecific fixation,<sup>2</sup> and greater specific fixation by antibody and extract.<sup>3</sup> Table II gives the antigenic units of nine extracts titrated in a refrigerator at 8° C. for eighteen hours and in a water bath at 37° C. for one hour; in every instance the unit was from two to eight times less in the refrigerator series.

For this reason *the primary incubation of antigen, antibody serum and complement in the titration of antigen should be exactly the same as used in the main complement-fixation tests.*

*The Influence of Method of Diluting Extracts with Saline Solution.*—Numerous experiments with different extracts have been conducted on this important subject; as previously described, four different emulsions were prepared with each extract. Each emulsion was titrated for the antigenic unit with two kinds of primary incubation, one hour at 37° C. and eighteen hours at 8° C.

The results of several experiments are given in Tables XVII, XVIII, XIX and may be summarized as follows:

1. As a general rule turbid emulsions prepared by adding saline very slowly to extracts or extracts very slowly to saline, were slightly more antigenic than opalescent emulsions prepared by rapid mixture of extracts and saline.

2. Emulsions prepared by slowly adding extract to saline were not as turbid as emulsions prepared by slowly adding saline to extract; the former were opalescent rather than turbid but equally antigenic. Since the latter were less anticomplementary we have concluded that *antigens are best diluted for complement-fixation tests by slowly adding the extract to the saline and shaking gently after each addition.*

TABLE XVII

THE INFLUENCE UPON ANTIGENIC ACTIVITY OF MANNER OF DILUTING TISSUE EXTRACTS WITH SALINE SOLUTION; PRIMARY INCUBATION 18 HOURS AT 8° C.

METHOD OF DILUTING	ANTICOMPLEMENTARY UNITS 1:10		
	ANTIGEN I*	ANTIGEN II	ANTIGEN III
Saline added drop by drop	1:50	1:50	1:200
Saline added very rapidly	1:100	1:25	1:100
Extract added drop by drop	1:200	1:50	1:200
Extract added very rapidly	1:200	1:50	1:200

\*Antigen I—cholest. and lecithin. alc. ext. beef heart; II—cholest. alc. ext. beef heart; III—acetone insoluble lipoids of beef heart.

TABLE XVIII

THE ANTIGENIC UNITS OF VARIOUS EXTRACTS DILUTED 1:50 WITH SALINE SOLUTION IN FOUR METHODS AND TITRATED WITH A PRIMARY INCUBATION OF 18 HOURS AT 8° C.

EXTRACTS	METHODS OF PREPARING EMULSIONS			
	SALINE ADDED SLOWLY	SALINE ADDED RAPIDLY	EXTRACT ADDED SLOWLY	EXTRACT ADDED RAPIDLY
No. 1 Plain alc. ext. human heart	0.08	0.1	0.08	0.1
No. 2 Plain alc. ext. beef heart	0.1	0.2	0.08	0.2
No. 3 Cholest. alc. ext. human heart	0.08	0.2	0.08	0.1
No. 4 Cholest. alc. ext. beef heart	0.08	0.2	0.1	0.2
No. 5 Acetone insoluble lipoids	0.04	0.06	0.04	0.06
No. 6 Cholest. and lecithin. ext. beef heart	0.04	0.04	0.2	0.04

TABLE XIX

THE ANTIGENIC UNITS OF VARIOUS EXTRACTS DILUTED 1:50 WITH SALINE SOLUTION IN FOUR METHODS AND TITRATED WITH A PRIMARY INCUBATION OF ONE HOUR AT 37° C.

EXTRACTS	METHODS OF PREPARING EMULSIONS			
	SALINE ADDED SLOWLY	SALINE ADDED RAPIDLY	EXTRACT ADDED SLOWLY	EXTRACT ADDED RAPIDLY
No. 1 Plain alc. ext. beef heart	0.7	1.2	0.2	0.4
No. 2 Plain alc. ext. human heart	0.5	0.8	0.6	0.8
No. 3 Cholest. alc. ext. beef heart	0.06	0.4	0.2	0.2
No. 4 Cholest. alc. ext. human heart	0.3	0.6	0.2	0.4
No. 5 Acetone insoluble lipoids	0.04	0.03	0.03	0.08
No. 6 Acetone insoluble lipoids	0.03	0.03	—	—
No. 7 Cholest. and lecithin. ext. beef heart	0.3	0.06	0.08	0.5
No. 8 Cholest. and lecithin. ext. beef heart	0.015	0.02	—	—

*The Relation of Serum.*—The amount of syphilitic serum to employ in these titrations is a matter of considerable importance; also the strength of the serum in syphilitic antibodies. Most serologists use 0.1 or 0.2 c.c. of strongly positive serum; others use similar quantities of moderately positive serum.

A large number of experiments have been conducted on this phase of the problem<sup>10</sup> leading to the following conclusions:

1. A mixture of several syphilitic sera is preferable to the use of a serum from a single individual.

2. Sera yielding strongly positive reactions are to be preferred because the unit is better defined.

3. If one amount of serum as 0.1 or 0.2 c.c. is being employed in the main tests a similar amount should be used in the antigen titrations; if the main tests are being conducted with varying amounts of serum the average should be used.

4. The sera should be free of anticomplementary activity and heated in exactly the same manner as in the main complement-fixation tests.

*The Influence of Heating.*—Heating saline emulsions of extracts in a water bath at 56° C. for thirty minutes does not increase antigenic activity (Table XX); boiling the alcoholic extracts for an hour with reflux condensers produces no change in antigenic activity except a slight loss with an occasional extract (Table IX).

TABLE XX

THE INFLUENCE OF HEATING EXTRACTS AT 56°C. FOR THIRTY MINUTES UPON ANTIGENIC ACTIVITY

EXTRACTS	UNHEATED	HEATED
Plain alc. ext. beef heart	0.1(1:300)	0.1(1:300)
Cholest. alc. ext. beef heart	0.1(1:300)	0.1(1:300)
Acetone insoluble lipoids	0.1(1:500)	0.1(1:500)
Cholest. and lecithin. ext. beef heart	0.1(1:600)	0.1(1:600)

*The Influence of Filtration.*—As previously stated, the filtration of small amounts of saline emulsions of various extracts through small, chemically clean and sterile Kitasato earthen filters removes the antigenic substances (Table XXI) as well as the anticomplementary and hemolytic substances.

TABLE XXI

THE INFLUENCE OF FILTRATION OF 1:5 DILUTIONS OF EXTRACTS UPON ANTIGENIC ACTIVITY

EXTRACTS	BEFORE FILTRATION	AFTER FILTRATION
Plain alc. ext. beef heart	0.1(1:100)	—*
Cholest. alc. ext. beef heart	0.1(1:200)	—
Acetone insoluble lipoids	0.1(1:200)	—
Cholest. and lecithin. ext. beef heart	0.1(1:400)	—

\*Not antigenic in 0.1 c.c. of 1:25, the largest amount tested.

#### PRINCIPLES FOR THE TITRATION OF ANTIGEN

The results of these studies have enabled us to formulate the following principles governing the titration of antigens for complement-fixation tests in syphilis:

*Hemolytic System.*—This should be exactly the same as employed in the main complement-fixation tests. The complement should be prepared in the same manner and used in the same number of units; likewise the hemolysin and corpuscles and the total volume should be the same.

*Anticomplementary Titration.*—(a) Emulsions should be prepared by adding the extract *slowly* drop by drop from a 1 c.c. pipette to the measured amount of saline and shaking gently. (b) Fresh non-syphilitic serum should be used; a mixture of sera is preferable in order to equalize the content of natural hemolysins. The serum should be heated in exactly the same manner as in the main tests and used in an average amount. (c) The mixtures of antigen, serum and complement should be given exactly the same primary incubation as used in the main complement-fixation tests; also receive the same amounts of hemolysin and corpuscles and secondary incubation. (d) The titration should be conducted with increasing amounts of a given emulsion with constant amounts of serum and complement *to ascertain the smallest amount of extract just producing beginning inhibition of hemolysis which is designated as the unit.*

*Hemolytic Titration.*—(a) An average amount of *heated* human or guinea pig serum should be used. (b) Increasing amounts of antigen emulsion with a constant amount of serum and corpuscles should be incubated in exactly the same manner as the secondary incubation of the main complement-fixation tests *to ascertain the smallest amount of extract just producing beginning hemolysis which is designated as the unit.*

*Antigenic Titration.*—(a) Emulsions should be prepared by adding the extract *slowly* drop by drop from a 1 c.c. pipette to the measured amount of saline and shaking gently. (b) A mixture of strongly positive syphilitic sera should be used; this serum should be heated in exactly the same manner as in the main tests and used in an average amount. (c) The mixtures of antigen, serum and complement should be given exactly the same primary incubation as used in the main complement-fixation tests; also receive the same amounts of hemolysin and corpuscles and secondary incubation. (d) The titration should be conducted with increasing amounts of antigen with constant amounts of serum and complement *to ascertain the smallest amount of extract giving complete inhibition of hemolysis which is designated as the unit.*

Details of the technic including the controls employed in a proposed standardized complement-fixation test are given in a separate article.<sup>11</sup>

#### CONCLUSION

1. The temperature and time of primary incubation of antigen, serum and complement, have a marked influence upon the results of anticomplementary, hemolytic and antigenic titrations of antigens.

2. In conducting the anticomplementary and antigenic titrations the primary incubation should be exactly the same as employed in the main complement-fixation tests; in the hemolytic titration the incubation should be the same as employed in the secondary incubation of the main tests.

3. As a general rule turbid emulsions of alcoholic extracts in saline solution prepared by adding saline solution very slowly to the extract, were more anticomplementary than opalescent emulsions prepared by rapidly mixing extract and saline.

4. Turbid emulsions were usually slightly more antigenic than opalescent emulsions.

5. The manner of preparing emulsions had no influence upon the hemolytic activity of alcoholic extracts.

6. Emulsions prepared by slowly adding the extract drop by drop or in small measured amounts to saline solution were less anticomplementary and equally antigenic as turbid emulsions prepared by adding the saline slowly to the extract; for these reasons emulsions should be prepared by slowly adding extract to saline solution.

7. Serum greatly reduces the hemolytic activity of saline emulsions of alcoholic extracts of tissues and should be included in titrations for hemolytic activity.

8. Filtration of saline emulsions of alcoholic extracts of tissues through chemically clean and sterile earthen filters removes the anticomplementary, antigenic and hemolytic substances.

9. Heat has very slight influence upon the properties of alcoholic extracts of tissues and does not serve for the removal of anticomplementary and hemolytic substances.

10. The unit of anticomplementary activity should be the smallest amount of antigen producing beginning inhibition of hemolysis rather than complete inhibition; the unit of hemolytic activity should be the smallest amount producing beginning hemolysis rather than complete

hemolysis and the unit of antigenic activity should be the smallest amount producing complete inhibition of hemolysis with a fixed amount of a mixture of syphilitic sera.

The principles governing the technic of anticomplementary hemolytic and antigenic titrations of alcoholic extracts of tissues for a standardized complement-fixation test are given.

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## STUDIES IN THE STANDARDIZATION OF THE WASSERMANN REACTION, XXVIII\*

### A STUDY OF FACTORS INFLUENCING THE AMOUNT OF ANTIGEN TO EMPLOY IN COMPLEMENT-FIXATION TESTS IN SYPHILIS

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(Received for publication November 30, 1920.)

THE amount of antigen employed in complement-fixation tests in syphilis is equally important as the kind of antigen; different methods are in use for determining the amount of antigen to employ and these as well as the use of different kinds of antigen are largely responsible for the variation in specificity and sensitiveness of complement-fixation tests in different laboratories.

Some serologists apparently do not hesitate to use an antigen according to the results of titrations essentially different from the technic of their complement-fixation test and indeed, may use an antigen in an arbitrary amount with inadequate or no preliminary titration at all; these practices cannot yield *uniformly* good and satisfactory results.

#### ANALYSIS OF METHODS FOR DETERMINING THE AMOUNT OF ANTIGEN TO EMPLOY

A variety of methods are being used to determine the proper amount of antigen to employ in Wassermann tests, which may be classified somewhat as follows:

*First Method.*—To determine the anticomplementary unit and use one-half or less this amount as the dose of antigen for the main tests. Wassermann advocated the use of one-half the largest amount of antigen which itself was found to be not at all anticomplementary; subsequent workers employ one-half to one-sixth of the anticomplementary unit.

With cholesterolized antigens most workers use from one-quarter to one-sixth the anticomplementary units to avoid nonspecific reactions; even a wider margin as one-tenth or more is advisable.

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\*Investigation aided by funds accruing from the preparation of arsphenamine.

Many excellent and careful workers have found this simple method for determining the dose of antigen satisfactory; however, it would appear defective by reason of the fact that the substances in an antigen responsible for the anticomplementary effects may not be antigenic. An extract used in a fraction of its anticomplementary unit may not be sufficiently antigenic and this is particularly true of plain alcoholic extracts of syphilitic liver. Furthermore, it would appear a good principle *to avoid the use of an unnecessarily large amount of antigen* as may be represented by a cholesterolized extract in one third of its anticomplementary unit; this would lessen the danger of nonspecific reactions and indeed, under certain conditions, a large amount may not be as antigenic as smaller amounts as shown by L'Esperance and Coca<sup>1</sup> and Ottenberg.<sup>2</sup>

*Second Method.*—With the above method a fixed amount of complement is employed in the titration with varying amounts of antigen; an entirely different principle is used by those who titrate the complement in the presence of the antigen, as Thomsen, Boas, Thomas and Ivy and others. These workers use a more or less fixed and arbitrary amount of antigen and adjust the complement to this amount; in other words, the adjustment is not of antigen to complement, but of complement to antigen.

As stated in a former article,<sup>3</sup> we have adopted the principle of titrating the complement in the presence of the dose of antigen, but not of a fixed and arbitrary amount because this fixed amount may actually prove too much or too little for the best work.

*Third Method.*—To determine the antigenic and anticomplementary units and use two or more antigenic units as the dose of antigen provided this amount is not more than one-third the anticomplementary and hemolytic units. This method is more accurate as it tends to avoid the use of excessive amounts of antigen and of worthless antigens. It is open to the objection of being based upon titration with a certain serum which may yield a unit unsuitable for other sera; however, by titrating with a mixture of syphilitic sera and using two or more antigenic units as the dose for the main tests, this objection is readily overcome.

#### PURPOSES FOR INVESTIGATION

The purpose of this investigation was to study the principles governing the *optimum amount of antigen to employ for the most sen-*



sitive specific complement-fixation test for syphilis; the technic employed in a study of this character is a matter of considerable practical importance. This investigation was based upon the principles governing the titration of antigen previously described<sup>4</sup> and with the hemolytic system and technic proposed for a standardized complement-fixation technic,<sup>5</sup> which includes a primary incubation of eighteen hours at 8° C.

### Part 1

#### ANTIGENIC SENSITIVENESS IN RELATION TO ANTICOMPLEMENTARY ACTIVITY

A principle established by Wassermann and followed by serologists generally, is to employ the largest amount of antigen in order to secure the most sensitive specific reactions; the unsafe amount is the anticomplementary and hemolytic units and the safe amount, the largest fraction of these which avoids nonspecific reactions. The question arises, do these large amounts of antigen as one-half to one-quarter the anticomplementary amounts represent the optimum amounts for complement-fixation tests?

With the principle of Wassermann's technic employing a fixed and arbitrary amount of complement, the answer would appear to be in the affirmative. In all of my experiments using one-half, one-third, one-fourth, one-fifth, one-sixth and higher fractions of the anticomplementary units of various antigens with a *fixed amount of complement in the antigen titrations and main tests*, the strongest reactions were observed with the larger amounts of antigen, none of the antigens being hemolytic in the doses employed.

The results summarized in Table I were observed with one serum in a series of experiments using the technic of Wassermann's test, including 0.1 c.c. of undiluted guinea-pig serum as the fixed dose of complement. The anticomplementary activity of each antigen was determined and fractions of these amounts used in tests employing amounts of syphilitic serum varying from 0.1 to 0.0125 c.c. The table gives the smallest amount of serum yielding a ++++ reaction and these amounts were always least with the largest amounts of antigen. In these tests I could find no evidence of the prezone reaction, that is, stronger reactions with the smaller amounts of antigen.

Similar results were observed with other antigens and syphilitic

TABLE I  
THE RELATION OF ANTIGENIC SENSITIVENESS OF ANTIGENS TO ANTICOMPLEMENTARY ACTIVITY IN TESTS CONDUCTED AFTER THE ORIGINAL WASSERMANN TEST

ANTIGENS	ANTICOMPL. UNITS 1:10	SMALLEST AMOUNT OF SYPHILITIC SERUM GIVING +++ REACTIONS				
		WITH 1/2 ANTICOMPL. UNIT	WITH 1/4 ANTICOMPL. UNIT	WITH 1/6 ANTICOMPL. UNIT	WITH 1/10 ANTICOMPL. UNIT	WITH 1/20 ANTICOMPL. UNIT
Ale. ext. syph. liver	1.2 c.c.	—*	—	—	—	—
Cholest. ext. beef heart	1.2 c.c.	0.05	0.05	0.05	0.1	—
Acetone insol. lipoids	1.2 c.c.	0.05	0.1	—	—	—
Cholest. and lecithin. extract beef heart	2.0 c.c.	0.05	0.05	0.05	0.1	—

\*Incomplete fixation with 0.1 c.c. serum (maximum amount used).

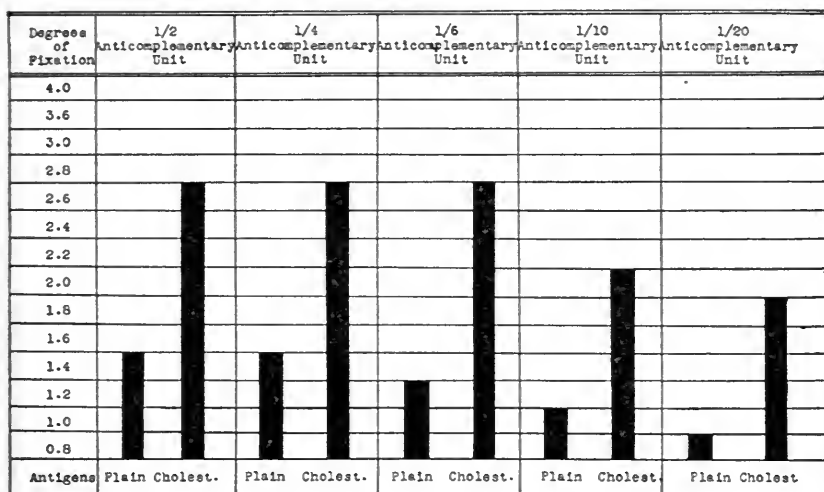
TABLE II  
THE RELATION OF DOSE OF ANTIGEN OF ACETONE INSOLUBLE LIPOIDS TO DEGREE OF COMPLEMENT FIXATION; PREZONE REACTION

ANTIGEN	UNIT COMPLEMENT 1:30	RESULTS WITH SYPHILITIC SERUM									
		0.1	0.05	0.025	0.0125	0.006	0.003	0.0015	0.00075	0.0003	
0.1 c.c. 1:10	0.4 c.c.	4	4	4	4	3	2	—	—	—	
0.1 c.c. 1:20	0.25 c.c.	4	4	4	4	4	3	1	1	—	
0.1 c.c. 1:40	0.25 c.c.	4	4	4	4	4	3	2	1	—	
0.1 c.c. 1:80	0.2 c.c.	4	4	4	4	4	1	1	—	—	

sera as shown in Chart 1 which gives a summary of reactions with twenty-four syphilitic sera tested with a plain and cholesterolized alcoholic extract of beef heart used in one-half, one-fourth, one-sixth, one-tenth and one-twentieth anticomplementary units.

In my experience if complement-fixation tests are conducted with a fixed amount of complement and a fraction of the anticomplementary unit of antigen after the original Wassermann test, plain extracts should be used in one-half to one-quarter, and cholesterolized extracts in one-sixth, of their anticomplementary units.

Chart 1.- The Relation of Anticomplementary Units of Plain and Cholesterolized Extracts to the Degree of Complement Fixation in Syphilis with a Primary Incubation of One Hour in a Water Bath.



However, the method of arbitrarily adopting a fraction of the anti-complementary unit of an antigen as a dose for syphilis complement-fixation tests cannot be recommended for at least two reasons:

First, some antigens and particularly plain alcoholic extracts of syphilitic liver and beef or human heart muscle, may not be antigenic even in doses equal to one-half the anticomplementary units. This is particularly true if tests are conducted with a primary incubation of one hour in a water-bath as shown in Table I with the alcoholic extract of syphilitic liver. It is not true, however, with a refrigerator incubation which increases the degree of complement fixation; neither is it true of cholesterolized extracts with either form of primary incubation.

Secondly, the method may result in the use of a needlessly large amount of antigen and with cholesterolized extracts greatly increases the chances of nonspecific reactions. For example, as shown in Tables VII, VIII and IX, one-quarter to one-sixth of the anticomplementary units of a number of different antigens resulted in just as much fixation of complement as one-half and one-third of the anticomplementary units. Of course this varies according to the kind of antigen and to the amount of syphilis antibody in a serum and for these reasons most serologists use one-third to one-sixth of the anticomplementary units in order to "pick up" weakly positive sera.

Since there is not necessarily a relation between the anticomplementary and antigenic activities of any antigen, a much better practice is to titrate for antigenic activity and use a sufficient number of antigenic units as a dose for complement-fixation tests.

*Prezone Reactions.*—Therefore when antigens are titrated and the complement-fixation tests conducted with a fixed and arbitrary amount of complement as in the original Wassermann test, strongest reactions with syphilitic sera invariably occur with the largest amounts of antigen. There may be no difference in the degree of fixation in tests employing one-half to one-quarter the anticomplementary units of antigen, but these amounts usually give stronger reactions than tests using one-sixth to one-tenth or smaller amounts of antigen.

When however, the complement is titrated in the presence of antigen and two units used in complement-fixation tests<sup>3</sup> different results may be observed with some antigens. L'Esperance and Coca<sup>1</sup> and Ottenberg<sup>2</sup> have shown that under these conditions a large dose of antigen (as one-half the anticomplementary unit) may give less fixation than a smaller dose (as one-tenth the anticomplementary unit).

We have conducted a large number of experiments with different antigens in a study of these prezone reactions and have found similar results with *an occasional antigen more anticomplementary than the average and consequently producing a relatively large unit of complement*. An example is shown in Table II with an antigen which was more anticomplementary than most extracts of acetone insoluble lipoids; the complement titrated in the presence of 0.1 c.c. of a 1:10 dilution gave a unit of 0.4 c.c. and when used in a dose of two units with this amount of antigen gave less fixation with a syphi-

litic serum than when the complement was titrated and the tests conducted with 0.1 c.c. of a 1:40 dilution of antigen.

As previously stated, I have observed the phenomenon with only an occasional extract and *sometimes it has occurred with one complement serum and not with a second*. As shown in Tables III, IV and V, a number of antigens showed no prezone reactions at all.

*Furthermore, when antigens are titrated by using dilutions with a constant dose of syphilitic serum and a constant dose of complement (two units titrated plain), prezone reactions have never been observed*. Table VI gives the results of titrations of four antigens with a primary incubation of eighteen hours at 8° C. As shown by these results prezone reactions do not occur under these conditions.

Briefly, my experiences with prezone reactions in relation to the very important practical subject of optimum dose of antigen for syphilis complement-fixation tests may be summarized as follows:

1. When antigens are titrated by using varying amounts of an emulsion with fixed amounts of complement and syphilitic serum prezone reactions do not occur; with extracts free of hemolytic activity in amounts as large as one-half the anticomplementary units, the strongest fixation reactions occurred with the largest amounts of antigen.

2. When complement-fixation tests are conducted by using a fixed and arbitrary amount of antigen with two units of complement titrated in the presence of this amount of antigen and varying amounts of syphilitic serum, prezone reactions *may* occur with *some* (not all) antigens; that is the larger amounts of syphilitic serum may give slightly less fixation of complement than the smaller amounts, which I believe is due to the influence of natural hemolysins. Reactions of this kind occur less frequently in tests with a refrigerator primary incubation than with a water-bath incubation.

3. When complement-fixation tests are conducted with varying amounts of antigen, the complement being titrated with each dose of antigen and used in two units with a fixed amount of syphilitic serum, the larger doses of antigen demanding the larger amounts of complement may yield weaker fixation reactions than the smaller amounts of antigen demanding less complement.

The last mentioned is the kind of prezone reaction described by L'Esperance and Coca and it is difficult to offer an explanation of this interesting phenomenon. Ottenberg believes that it is probable

TABLE III  
THE RELATION OF THE ANTICOMPLEMENTARY TO THE ANTIGENIC ACTIVITY OF ANTIGENS

EXTRACTS	SMALLEST AMOUNTS OF A SYPHILITIC SERUM GIVING ++++ REACTIONS WITH:				
	$\frac{1}{2}$ ANTICOMPL. UNIT	$\frac{1}{3}$ ANTICOMPL. UNIT	$\frac{1}{4}$ ANTICOMPL. UNIT	$\frac{1}{6}$ ANTICOMPL. UNIT	$\frac{1}{10}$ ANTICOMPL. UNIT
Plain alc. ext. beef heart	0.025	0.025	0.025	0.025	0.05
Cholest. alc. ext. beef heart	0.0125	0.0125	0.0125	0.0125	0.025
Alc. ext. syphilitic liver	0.025	0.025	0.025	0.025	0.05
Acetone insoluble lipoids	0.025	0.025	0.025	0.025	0.05
Cholest. and lecithin. ext. beef heart	0.025	0.025	0.025	0.025	0.025

TABLE IV  
THE RELATION OF THE ANTICOMPLEMENTARY UNIT OF AN ANTIGEN TO ANTIGENIC SENSITIVENESS

CHOLEST. AND LECITHIN. EXTRACT BEEF HEART*	UNIT OF COMPL.	SERUM NO. 1.					SERUM NO. 2				
		0.1	0.02	0.004	0.0008	0.00016	0.1	0.02	0.004	0.0008	0.00016
$\frac{3}{2}$ anticompl. unit	0.3 c.c.	4**	4	-	-	-	4	2	-	-	-
$\frac{1}{2}$ "	0.3 c.c.	4	4	-	-	-	4	2	-	-	-
$\frac{1}{4}$ "	0.3 c.c.	4	4	-	-	-	4	2	-	-	-
$\frac{1}{6}$ "	0.3 c.c.	4	4	-	-	-	4	2	-	-	-
$\frac{1}{8}$ "	0.25 c.c.	4	4	-	-	-	4	3	-	-	-
$\frac{1}{10}$ "	0.25 c.c.	4	4	-	-	-	3	2	-	-	-
$\frac{1}{20}$ "	0.25 c.c.	4	4	-	-	-	2	1	-	-	-
$\frac{1}{30}$ "	0.25 c.c.	4	4	-	-	-	1	-	-	-	-
$\frac{1}{50}$ "	0.25 c.c.	2	1	-	-	-	1	-	-	-	-
$\frac{1}{100}$ "	0.2 c.c.	1	-	-	-	-	-	-	-	-	-
$\frac{1}{200}$ "	0.2 c.c.	1	-	-	-	-	-	-	-	-	-
$\frac{1}{500}$ "	0.2 c.c.	-	-	-	-	-	-	-	-	-	-

\*Anticomplementary unit was 0.4 c.c. of 1:5 dilution.

\*\*4—++++; 3—+++; 2—++; 1—+.

TABLE V  
THE RELATION OF THE ANTICOMPLEMENTARY UNITS OF EXTRACTS TO ANTIGENIC SENSITIVENESS

EXTRACTS	WITH 1/2 ANTI-COMPLEMENTARY UNIT				WITH 1/3 ANTI-COMPLEMENTARY UNIT				WITH 1/4 ANTI-COMPLEMENTARY UNIT				WITH 1/10 ANTI-COMPLEMENTARY UNIT				WITH 1/20 ANTI-COMPLEMENTARY UNIT			
	0.1	0.02	0.004	0.0008	0.00016	0.1	0.02	0.004	0.0008	0.00016	0.1	0.02	0.004	0.0008	0.00016	0.1	0.02	0.004	0.0008	0.00016
Plain alc. ext. beef heart.....	4*	4	4	—	—	4	4	4	—	—	4	4	4	—	—	4	4	3	—	—
Cholest. alc. ext. beef heart....	4	4	4	3	—	4	4	4	3	—	4	4	4	1	—	4	4	4	—	—
Acetone insoluble lipoids .....	4	4	4	—	—	4	4	4	—	—	4	4	4	—	—	4	4	4	—	—
Cholest. and lecithin ext. beef heart.....	4	4	4	—	—	4	4	4	—	—	4	4	4	—	—	4	4	4	—	—

\* 4 = +++++; 3 = ++++; 2 = ++; 1 = +

TABLE VI  
THE TITRATION OF ANTIGENS FOR ANTIGENIC ACTIVITY IN REFERENCE TO PREZONE REACTIONS

ANTIGENS	ANTIGENS USED IN 0.1 C.C. OF											
	1:20	1:40	1:80	1:100	1:200	1:400	1:600	1:800	1:1000	1:2000		
Plain alc. ext. beef heart	4	4	3	3	3	1	—	—	—	—		
Cholest. alc. ext. beef heart	4	4	4	4	4	3	2	2	2	1		
Acetone insoluble lipoids	4	4	4	4	4	4	3	3	1	—		
Cholest. and lecithin ext. beef heart	4	4	4	4	4	4	3	3	3	1		

"when the dose of antigen is increased beyond a certain point the amount of complement which has to be added to overcome the anti-complementary effect is too great to be fixed by certain grades of positive serum."

This explanation may be correct but I also suspect that the larger amounts of complement introduce more natural antisheep hemolysins which result in an increase of hemolysis and the masking of fixation of complement by syphilis antibody and antigen.

## Part 2

### THE NUMBER OF ANTIGENIC UNITS OF ANTIGEN IN RELATION TO COMPLEMENT FIXATION IN SYPHILIS

In the technic adopted for the titration of antigen in a proposed standardized complement-fixation test,<sup>5</sup> the antigen is titrated by using varying amounts of an emulsion with 0.05 c.c. of a mixture of syphilitic sera and two units of complement titrated plain, that is, in the absence of antigen; with this technic the content of natural antisheep hemolysin is the same in all tubes, prezone reactions do not occur and there is not the slightest difficulty in deciding upon the smallest amount of antigen giving a +++ reaction, which is taken as the antigenic unit.

With this technic the question arises how many antigenic units should be used as an optimum dose of antigen for the most *sensitive specific reactions*? Only experience based upon numerous experiments can give the answer; furthermore, all experiments must be conducted with a uniform technic.

The antigenic unit of an antigen varies according to the amount of syphilitic serum and kind of primary incubation, used in the titration; *the technic employed in these experiments* is fully described elsewhere<sup>4, 5, 6</sup> but it may be stated here that in the antigenic titrations 0.05 c.c. of a mixture of syphilitic sera was employed (which is one-half the maximum amount used in the main tests) *with a primary incubation of eighteen hours at 8° C.*

Numerous experiments have been conducted by using antigens in from one to fifty antigenic units in complement-fixation tests, the results of a few being given in Tables VII and VIII and Charts 2 and 3.

The general result of these experiments has shown *that the optimum amount of antigen is from five to fifteen antigenic units* depending



TABLE VII

THE RELATION OF AMOUNT OF ANTIGEN IN ANTIGENIC UNITS TO ANTIGENIC SENSITIVENESS

CHOLEST. AND LECTIN. EXT. BEEF HEART	UNIT OF COMPLEMENT 1:30 C.C.	SYPHILITIC SERUM				
		0.1	0.02	0.004	0.0008	0.00016
		1	—	—	—	—
1 antigenic unit	0.2	3	—	—	—	—
2 antigenic units	0.2	3	—	—	—	—
3 antigenic units	0.25	4	—	—	—	—
4 antigenic units	0.25	4	—	—	—	—
5 antigenic units	0.25	4	—	—	—	—
8 antigenic units	0.25	4	—	—	—	—
10 antigenic units	0.25	4	—	—	—	—
20 antigenic units	0.4	1	—	—	—	—

\* Antigenic unit was 0.1 c.c. of 1:400 dilution; anticomplementary unit was 0.4 c.c. of 1:5 dilution.

TABLE VIII

THE RELATION OF UNITS OF ANTIGEN TO DEGREE OF COMPLEMENT FIXATION\*

UNITS OF ANTIGEN	SYPHILITIC SERUM 1						SYPHILITIC SERUM 2					
	0.1	0.05	0.025	0.0125	0.006	0.003	0.1	0.05	0.025	0.0125	0.006	0.003
1	3**	3	2	—	—	—	2	1	1	—	—	—
2	3	3	2	1	1	—	2	1	1	—	—	—
3	3	3	2	1	—	—	3	1	1	—	—	—
4	4	3	2	1	—	—	3	1	1	—	—	—
5	4	4	3	1	—	—	3	1	1	—	—	—
6	4	4	3	1	—	—	4	2	1	—	—	—
7	4	4	3	2	—	—	4	2	1	—	—	—
8	4	4	3	2	—	—	4	2	1	—	—	—
9	4	4	3	2	—	—	4	2	1	—	—	—
10	4	4	4	2	—	—	4	3	1	—	—	—
12	4	4	4	2	—	—	4	3	1	—	—	—
15	4	4	4	3	1	—	4	4	3	1	—	—

\*Cholest. and lecithin. alc. ext. beef heart employed.

\*\*4—++++; 3—+++; 2—++; 1—+.

upon the kind of antigen. With plain alcoholic extract at least ten to fifteen antigenic units should be used as the optimum amount of antigen; with cholesterolized extracts and the new antigen of cholesterolized (0.2 per cent) and lecithinized alcoholic extract of beef heart, ten antigenic units usually represents the optimum dose (Charts 2 and 3).

As shown in Tables IV, VII and IX, the units of complement titrated in the presence of one to twenty units of antigen are smallest with amounts of antigen under four antigenic units; with five to ten

TABLE IX

THE INFLUENCE OF AMOUNT OF EXTRACT UPON THE TITRATION OF COMPLEMENT

CHOLEST. ALC. EXT. BEEF HEART	UNIT OF COMPLEMENT NO. 1 DILUTED 1:30		UNIT OF COMPLEMENT NO. 2 DILUTED 1:30	
	WATER-BATH*	REFRIGERATOR**	WATER-BATH*	REFRIGERATOR**
1 unit	0.12 c.c.	0.2 c.c.	0.12 c.c.	0.18 c.c.
2 units	0.15 c.c.	0.25 c.c.	0.12 c.c.	0.2 c.c.
3 units	0.2 c.c.	0.4 c.c.	0.15 c.c.	0.3 c.c.
4 units	0.2 c.c.	0.4 c.c.	0.15 c.c.	0.3 c.c.
6 units	0.2 c.c.	0.4 c.c.	0.15 c.c.	0.3 c.c.
8 units	0.25 c.c.	0.45 c.c.	0.18 c.c.	0.4 c.c.
10 units	0.25 c.c.	0.5 c.c.	0.18 c.c.	0.5 c.c.
20 units	0.4 c.c.	0.8 c.c.	0.2 c.c.	0.17 c.c.

\*Complement and antigen incubated in water-bath for one hour before addition of hemolysin and corpuscles.

\*\*Complement and antigen incubated in refrigerator for eighteen hours before addition of hemolysin and corpuscles.



units of antigen the complement unit remains quite stationary, but with amounts of antigen as high as twenty or more antigenic units, the unit of complement becomes higher and higher and reduces the sensitiveness of complement-fixation tests conducted with two units either by introducing too much natural hemolysin in the large doses of complement or because these large amounts of complement are not fixable by certain syphilitic sera.

The majority of extracts of acetone insoluble lipoids, alcoholic extracts of heart re-enforced with 0.2 per cent cholesterol and the new antigen of alcoholic extract of heart re-enforced with 0.2 per cent cholesterol and lecithins, are antigenic in 0.1 c.c. of dilutions 1:200 to 1:500 and anticomplementary in from 0.3 to 0.5 c.c. of 1.5 dilutions; the antigenic unit is therefore, at least one hundred times and a dose of ten units at least ten times, less than the anticomplementary unit. *Experience has shown that a dose of ten antigenic units yields very sensitive and specific reactions in the technic to be proposed as a standardized complement-fixation test and is the amount of antigen proposed as an optimum dose.* This dose must be, however, at least five to ten times less than the anticomplementary and hemolytic units; otherwise the antigen should not be used. Experience has shown that with the new antigen the dose employed (ten units) is usually more than ten times less than the anticomplementary and hemolytic units.

#### SUMMARY AND CONCLUSIONS

1. The methods employed for titrating antigen and conducting complement-fixation tests influence the amount of antigen to employ as the optimum dose for the most sensitive and specific reactions.

2. When antigens are titrated and used in fixation tests with a fixed amount of complement as in the original Wassermann test, the degree of fixation by syphilitic serum is in proportion to the amount of antigen employed; that is, tests conducted with one-half to one-sixth the anticomplementary units of antigens yield stronger reactions than tests using smaller amounts of antigen.

3. There is no constant relation between the anticomplementary and antigenic properties of antigens; an antigen used in an amount as large as one-half of its anticomplementary unit, may not prove perfectly antigenic and particularly plain extracts tested with water-bath incubation. For this reason and because the practice of using a

fraction of the anticomplementary unit may introduce an unnecessarily large dose of antigen, it is better to titrate for antigenic activity and use a certain number of antigenic units.

4. With the methods proposed as a standardized technic for titrating antigen and conducting complement-fixation tests for syphilis, the optimum dose of antigen varies from five to fifteen antigenic units depending upon the kind of antigen.

5. When complement is titrated in the presence of antigen and used in two units in fixation tests, reactions with syphilitic serum may be stronger with small amounts of antigen than with large amounts (prezone reactions). This is particularly true of antigens more anticomplementary than usual; it has not been observed with all antigens but only with a few.

6. Prezone reactions have been observed with some complements and not with others; they are believed to be due to the influence of natural hemolysins in the larger amounts of complement demanded to overcome the anticomplementary activity of the larger amounts of antigen or to non-fixability of these large amounts of complement by certain syphilitic sera.

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## QUANTITATIVE COMPLEMENT-FIXATION TEST IN SYPHILIS

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(Received for publication, May 5, 1922)

IN my paper titled "A New Complement-Fixation Test for Syphilis Based upon the Results of Studies in the Standardization of Technic" recently published in the American Journal of Syphilis (January, 1922) the following amounts of serum were advised for the conduct of the quantitative test:

0.1 c.c.  
0.02 c.c.  
0.004 c.c.  
0.002 c.c.  
0.001 c.c.  
0.1 c.c. (control)

In the experience of others and ourselves the drop from 0.02 c.c. to 0.04 c.c. is too great for securing a satisfactory quantitative reaction with some sera as, for example, in reactions as follows: + + + +, + + + +, -, -, - (44 ---).

The following method has been used for several months and found entirely satisfactory. The variations in amounts of serum are not as great, the last dose is larger and the dilutions are set up more rapidly. On the basis of the results of a large number of comparative tests, I wish to make this change in the quantitative test and advise the use of the following amounts of each serum as employed by Detweiler<sup>1</sup> in his quantitative test except that I do not employ a 0.2 c.c. dose:

0.1 c.c.  
0.05 c.c.  
0.025 c.c.  
0.005 c.c.  
0.0025 c.c.  
0.1 c.c. (control)

Otherwise the technic is exactly as described. The following method is advised for setting up these amounts of serum:

(a) Place 1.2 c.c. of saline solution in tube No. 1 of each set; this is quickly accomplished by placing 1 c.c. in these tubes by means of a 10 c.c. pipet and following with the addition of 0.2 c.c. with a 1 c.c. pipet.

Place 0.5 c.c. of saline in tubes 2, 3, and 5 of each set.

Place 2 c.c. of saline in tube No. 4 of each set.

(b) Place 0.3 c.c. of serum in tube No. 1; mix and transfer 0.5 c.c. to tubes No. 2 and 6.

Mix No. 2 and transfer 0.5 c.c. to No. 3.

Mix No. 3 and transfer 0.5 c.c. to No. 4.

Mix No. 4 and transfer 0.5 c.c. to No. 5; discard 1.5 c.c.

Mix No. 5 and discard 0.5 c.c.

This leaves 0.5 c.c. in each of the six tubes of a set carrying the amounts of serum given above.

The results are recorded according to the degree of inhibition of hemolysis in each tube as described in my paper. The clinical interpretations are as follows:

*Very strongly positive* when there is fixation of any degree in the first four or all five tubes (the sixth tube is the serum control).

*Strongly positive* when there is fixation in the first three tubes.

*Moderately positive* when there is fixation in the first two tubes.

*Weakly positive* when there is fixation in the first tube.

*Negative* when hemolysis is complete.

As stated in my paper, complement fixation is sometimes less in the first tube than in the second tube. Detweiler<sup>2</sup> has previously described this phenomenon and ascribed it to the presence of natural antisheep hemolysin but I have observed it in tests employing an antihuman and antichickens hemolytic systems and believe that some other serum constituent is responsible for interference with complement fixation. At any rate when this occurs the interpretation of the reaction is unchanged; for example a reaction showing +, +++, +, -, - would be interpreted as strongly positive and a reaction -, ++, -, -, - is interpreted as moderately positive because fixation occurred in the second tube.

*It is very important to note however, that this phenomenon may be responsible for falsely negative reactions in ordinary complement-fixation tests employing 0.1 or 0.2 c.c. serum as commonly practiced. For this reason it is advisable to routinely employ varying amounts*

*of each serum because a small amount of serum as 0.05 c.c. may yield a positive reaction, when larger amounts as 0.1 or 0.2 c.c. may not; this is true not only of my test but of other tests as well and constitutes an important reason for using varying amounts of each serum for the purpose of securing the best results.*

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## THE WASSERMANN REACTION FROM THE CLINICIAN'S POINT OF VIEW

(BASED ON THE COMPARISON OF MORE THAN 1700 SEROLOGICAL  
EXAMINATIONS)

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(Received for publication, December 16, 1921.)

THERE is probably no one laboratory test that is of greater interest to the serologist, clinician and patient than the Wassermann reaction. There is no other test upon which at times so much depends, and which means so much to the patient as the Wassermann reaction. There is no laboratory test that has received more attention and consideration by the physician, and now by the public since the war, than the Wassermann reaction.

With all the literature on this subject, with all the time and study given to it, with all its modifications and checks, it still remains at times a very unbelievable and confusing test.

I wish to present my clinical experience in a series of 366 private patients, upon whom 1742 tests have been made. The tests were made by three different laboratories, which will be designated as Laboratories A, B, and C. All clinical examinations were done personally, and when it was found necessary, patients were referred to competent specialists for examinations of the eyes, nervous system, etc. The personal equation makes the clinical study more accurate and guards against confusion in the laboratory findings.

In view of the fact that the serologic reports of this series show a discrepancy of some degree in 36 per cent of the cases and variations of three plus or more in 25 per cent, I wish to emphasize the importance of the clinical examination. If every fourth laboratory test is going to bring us doubt and confusion, we must be ready to make a correct diagnosis regardless of the Wassermann report. We must decide whether a patient should marry, or, if married,

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\*Read before the Cincinnati Academy of Medicine, Nov. 28th, 1921.

whether he should have children. We must know whether the patient is cured or whether he needs further treatment.

Too much care cannot be given to the clinical examination. Carefully question your patient as to whether or not he has been infected. You will find that many patients are evasive and unwilling to cooperate with you on this particular point. Be ready for a positive diagnosis in spite of his apparently negative history. If he admits infection, find out how long he had the chancre and look for secondary symptoms as a rash, enlarged glands, sore throat, loss of hair, etc.

The history of previous treatment is extremely important, whether constitutional or local. This, as I will show later, affects the interpretation of the Wassermann report.

Many writers have concluded from their study of the relation between the clinician and the serologist that the only solution lies with the serologist. Wolbarst<sup>1</sup> says: "They must get together and perfect their technic in such a manner that we practitioners may with safety accept their reports on their face value without doubt or hesitation. . . . We must feel sure that all serologists will give us the same findings on the serum submitted to them." Ohlmacher,<sup>2</sup> before the Sioux Valley Medical Association, made a strong plea for the standardization of the Wassermann test. I believe with him that it, with its numerous modifications is the best single test that we have for syphilis. Many clinicians have come to rely upon the Wassermann test as a last resort. But when we realize that we cannot rely entirely upon that test, even when it is properly performed we do well to make certain that our clinical examination is unquestionably thorough. In the present series, I received a negative report from at least one of the laboratories on 52 patients from whom I had a definite history and positive therapeutic test of syphilis and who had received no adequate treatment.

Suppose I took the laboratory report as final, as many physicians do. I would allow these patients to go without treatment until the evidences of the disease were too obvious to be overlooked by the most trusting physician. By that time, the chance for rapid cure by intense treatment has slipped away. It is universally conceded that in its early stages, the Wassermann reaction is less likely to be positive. In other words, the blood changes which make the Wassermann reaction possible, are progressive with the duration

of the infection. Therefore, it is evident that the serologists must realize the responsibility they assume when they let a negative report go out. That is just as likely to be harmful as to permit a positive report to be issued for a patient who shows no evidence and gives no history of syphilitic infection.

The cases reported in the accompanying table show a discrepancy between my clinical findings and the serologic report in 114 cases. This does not include the known treated syphilitic cases which give a negative reaction, in at least two of the six tests, of these there were 98 cases.

I cannot emphasize too strongly, as I have many times reiterated, that if we expect to effect a cure, we must treat syphilitics while the Wassermann is still negative. An early negative Wassermann is gratifying. It shows that we still have time to treat with some assurance of success. By all means, do not be influenced to suspend treatment. Three years is the time limit in such cases and more may be necessary if the reaction becomes positive. The only possible way to prevent late cerebrospinal manifestations is by early, regular, energetic treatment. It is well also to remember that a great many cases of optic neuritis are found in negative Wassermann but known syphilitics (see Cases 18 and 48).

Undoubtedly a routine Wassermann test on all patients would be of benefit if the laboratory were strictly reliable. Since it is not, I have the test made only on all suspicious and positively luetic cases. A clean cut, clinical case of syphilis needs no serologic test, but it is better to have one done, to avoid criticism that may arise in the future either from the patient or any other physician who may be treating the case. At the same time, we must remember that a negative Wassermann in the presence of a suspicious lesion on the penis does not mean that the patient has not a hard chancre, and that a positive Wassermann does not necessarily mean that the patient has syphilis. It depends on the laboratory making the report and also upon the condition of the patient.

To make a positive diagnosis of syphilis on the laboratory findings alone in the absence of all clinical and historical evidence, as many physicians are doing today, I consider to be absolutely wrong, and unpardonable.

Before deciding that a man, woman or child is syphilitic, we must utilize every known method of testing, even if it is necessary

to study the patient for some time and send him to different specialists; I cannot condemn too strongly the practice of treating a case for syphilis, just because the blood was doubtful or weakly positive in the absence of a history of clinical manifestations. In such cases, one must not depend upon the report from one laboratory, or, what is worse, merely send the blood once.

I believe that if we come to the conclusion, after studying all the facts in the case, that our patient has syphilis, he should be treated for three or four years, even though his blood test is negative. Once we are convinced of the diagnosis, we must treat him as a pronounced case. What chance of a cure would three or four months of indifferent treatment give him?

Furthermore, if we ever expect to stamp out syphilis, and prevent its end results, we must begin to educate the public and tell our patients individually that one negative blood test on one who has suffered from syphilis without sufficient treatment means exactly nothing, and that he is not cured.

We, as physicians, must start right now to tell all our patients that one negative Wassermann alone does not mean a cure. I know of no other thing that is doing more to prevent the curing of syphilis than the statement "Negative Wassermann cured." Fourteen per cent of my cases show definite infection with negative Wassermans.

It is impossible to explain why this is so, but the fact is attested to by many other observers. Craig and Nichols<sup>3</sup> for instance, note that: "no dependence can be placed on a negative Wassermann reaction in individuals who have, within twenty-four hours of the collection of blood, ingested considerable amounts of alcohol, while in some instances the drug may render the reaction negative for as long as three days. Careful inquiry, therefore, should be made regarding recent use of alcohol before collecting serums for the complement-fixation test in lues."

Gradwohl<sup>4</sup> in presenting the Hecht-Weinberg-Gradwohl modification of the Wassermann technic draws attention to the fact that the amount of natural amboceptor in human serums seems to be responsible for making the Wassermann appear negative and a Hecht-Weinberg-Gradwohl positive in cases of ocular syphilis, cases that have received intensive but inadequate treatment and provocative cases.

Discussion of this modification has revealed that others have found it to be a more delicate test. In my series, this test was done together with the Wassermann on every specimen sent to Laboratory A. One-eighth of the reports show a stronger reaction in the former than in the latter test.

I do not wish to minimize or in any way lessen the value and importance of the Wassermann reaction, but I think the pendulum has swung too far toward the serologic test, and that the positive and negative clinical signs are being neglected. Also, the laboratory report is not the final word, but the clinician's word is, and must ever be, when dealing with human ills.

Only the other day, I saw a typical case of multiple gumma of the penis that had received no treatment for three months, because the laboratory reported negative blood findings. He received an intravenous injection of arsphenamine and at the same time I did my routine Wassermann test, sending it to three different laboratories. In justice to the Wassermann, I must say that all three reported positive.

About a year ago, I saw an initial lesion of the left cheek, secondary roseola, etc., on a recently married young woman, the wife of a young man whom I had known for years. She had gone from doctor to doctor receiving no treatment because her blood was negative. It had not had time to become positive when taken. Questioning her husband brought out a clear history of syphilis. He said he thought he was cured, but he had had no test for seven years. Examination of the mouth showed tongue and mucosa covered with mucous patches and ulcerations. Wassermann in both man and wife, when I examined them, was four-plus positive. I could relate case after case that, although not quite so striking as above, is, nevertheless, proof of the unreliability of the negative Wassermann.

For obvious reasons, the general practitioner, surgeon or specialist, generally speaking, cannot make the blood tests himself. He must depend for his report upon the serologist. This makes it all the more difficult for the clinician, as often the patient requests to see the report and help decide the question.

Quite often when a positive report is expected, we receive a negative one and vice-versa, or what is more exasperating ( $\pm$ ) doubtful report.

As a rule, the physician has the test made for one of four reasons:

1. To assist in diagnosis of a doubtful case.
2. To confirm an already positive diagnosis.
3. To determine the progress while the patient is under anti-syphilitic treatment.
4. To gratify the request of the patient. This is not an uncommon occurrence.

Of course, a positive reaction in one not suspected of syphilis gives the first clue to the trouble and cannot be valued too highly in some cases. However, are we sure that a positive reaction means syphilis in one in whom all clinical evidence is lacking?

Wile and Halsey<sup>5</sup> have concluded from their extensive studies that, while the positive Wassermann still stands as the greatest diagnostic aid in discovering syphilis, the ever increasing discrepancies reported with each refinement and the ever increasing number of permanently positive cases, previously regarded as negative, show that the Wassermann cannot be a guide to therapeutics. In view of the fact that the real nature of the reaction is so little understood, Wile and Halsey submit that the serologic and clinical cures are not necessarily parallel and that energy of treatment directed toward attempting to make a persistent positive react negatively may well not only be useless, but misdirected.

Strickler, Munson and Sidlich<sup>6</sup> have shown that nonsyphilitic patients will tend to give positive Wassermann reaction after intravenous therapy in the form of weekly injections of 0.5 gm. arsphenamine. Among the patients treated were cases of eczema, psoriasis, acne vulgaris and rosacea, vitiligo, purpura, sycosis vulgaris and some of the rarer skin affections.

Until a standard technic has been devised and accepted by the serologist and different laboratories, throughout the country it will be difficult to form an accurate comparison of the results of the Wassermann tests from one or different laboratories.

To illustrate from my own series; 14 per cent of the cases were reported negative from one laboratory and two or more plus in both tests from another laboratory; 16 per cent were reported as not more than one plus from one laboratory and four plus from a second laboratory. Out of 276 cases, 75 per cent were reported identically on all tests of which 233 were negative. One-fifth of the negative should have been positive according to their history and therapeutic

tests. On the first 266 cases, 132 were negatives, one-fourth should have been positive according to their history and therapeutic test.

Although my statistics show that these rules do not hold in all cases, my guide to the interpretation of the Wassermann reaction, as a general working basis, is as follows:

1. A four-plus reaction means syphilis; not, however, if the cholesterine antigen only is four plus.
2. A three-plus means syphilis.
3. A persistent two-plus means syphilis.
4. Anything below a two-plus, without any clinical symptoms or history of infection does not mean syphilis.
5. A negative reaction, without any clinical symptoms or history of infection means patient has not syphilis.

Kilduffe<sup>7</sup> claims that a positive reaction with a cholesterinized antigen of four-plus or three-plus is an indication of the presence of syphilis in the blood. I do not agree with this statement. Eight cases in the present series show that it is incorrect. A positive cholesterinized antigen alone, with no history or clinical signs of the disease, does not mean syphilis. Stokes<sup>8</sup> recently commented upon the too delicate reaction of this antigen. He says: "There is little doubt in my mind that a single antigen test with a highly cholesterinized preparation, while it identifies many concealed infections, will yield a surprising percentage of false positives."

Henes,<sup>9</sup> in his work on cholesterinemia in relation to the Wassermann reaction throws considerable light upon the unreliability of this fortified antigen. He believes that the reaction will vary depending on the measure of the cholesterinemia in a given case at the time of the withdrawal of the blood. In other words, "we must know and appreciate those conditions which influence the measure of the cholesterinemia both under normal and under pathologic conditions, and take them into consideration."

To illustrate the fallibility of the Wassermann test, I wish to present two cases of the present series which have been particularly perplexing.

CASE 31.—Mr. H. J. B. Primary and secondary syphilis. Sept. 23, 1916. Began treatment.

By Nov. 27 he had had three injections of old salvarsan and six injections of mercury.

On April 3, 1917, his Wassermann and Hecht-Weinberg were both four-plus.

TABLE I  
COMPARISON OF WASSERMANN REPORTS FROM DIFFERENT LABORATORIES\*

CASE NO.	LAB. A	LAB. B	LAB. C	CLINICAL DIAGNOSIS	REMARKS
1.	Wass. +	Alc. -	Alc. -	Tertiary syphilis; multiple gumma of the left arm.	Patient had no treatment; Wass. should have been strongly positive.
2.	H. W. +++	Chol. ++++	Alc. -	Not syphilitic.	
3.	H. W. -	Chol. -	Alc. -	Tertiary syphilis; ulcerative gumma of left testicle.	Case undiagnosed for one year; denies infection.
4.	Wass. ++++	Alc. ++++	Alc. ++++	Tertiary syphilis.	No symptoms present; no history of infection; wife had a frank case of syphilis four years ago.
5.	H. W. ++++	Chol. ++++	Chol. ++++		
6.	Wass. -	Alc. -	Alc. -	Not syphilitic.	
7.	H. W. -	Chol. -	Alc. -	Not syphilitic.	
8.	Wass. -	Chol. -	Alc. -	Not syphilitic.	
9.	H. W. -	Chol. -	Alc. -	Tuberculosis of throat.	
10.	H. W. -	Chol. -	Alc. -	Had syphilis but received treatment.	Thorough treatment.
11.	Wass. ++	Chol. -	Alc. -	Tertiary syphilis; cerebro-spinal.	Distinct history; had been under treatment.
12.	H. W. ++++	Chol. -	Alc. -	Carcinoma of the superior maxillary bone.	
13.	Wass. -	Chol. -	Alc. -	Syphilis.	Thorough treatment.
14.	H. W. -	Chol. -	Alc. -	Varicose leg ulcer.	
15.	H. W. -	Chol. -	Alc. -	Not syphilitic.	
16.	Wass. -	Chol. -	Alc. -	Syphilis; cerebrospinal.	Had received thorough treatment.
17.	H. W. -	Chol. -	Alc. -	Psoriasis.	Husband known case of syphilis; wife had never been treated.
18.	Wass. -	Chol. -	Alc. -	Secondary syphilis.	Husband, had frank case of syphilis; infected his wife Dec. 30, 1918; wife had been under continuous treatment when she developed a syphilitic neuritis although her Wass. was negative; intense anti-syphilitic treatment was continued and patient recovered from her eye condition; Wass. remained negative.



TABLE I—CONT'D.

CASE NO.	LAB. A	LAB. B	LAB. C	CLINICAL DIAGNOSIS	REMARKS
19.	Wass. - H. W. -	Ale. - Chol. -		Not syphilitic.	
20.	Wass. - H. W. -	Ale. - Chol. -		Not syphilitic.	
21.	Wass. ++ H. W. ++++	Ale. - Chol. ++++		Undetermined case of syphilis; indefinite history of infection; no symptoms.	Wass. on July 30, 1920, showed that he did not have syphilis. on Aug. 16, 1920, showed that he had syphilis. After treatment Wass. was negative; on Feb. 8 and 16, 1921, Wass. was negative to Lab. A and Lab. B, but Lab. C reported it positive.
22.	Wass. - H. W. -	Ale. - Chol. ++++		See Case 21.	
23.	Wass. ++++ H. W. ++++	Ale. ++++ Chol. ++++		Tertiary syphilis.	Syphilitic ulceration of tongue 23 years' duration; no history of ever infecting any one.
24.	Wass. ++++ H. W. ++++	Ale. ++++ Chol. ++++		Tertiary syphilis.	Ulcerative gumma of left arm.
25.	Wass. ++++ H. W. ++++	Ale. ++ Chol. ++++		Syphilis, insontium.	Ulcerated gumma of hard and soft palate; undiagnosed for three years.
26.	Wass. ++++ H. W. ++++	Ale. ++++ Chol. ++++		Syphilis, inherited.	Optic nerve changes.
27.	Wass. - H. W. -	Ale. - Chol. -		Not syphilitic.	
28.	Wass. ++++ H. W. ++++	Ale. ++++ Chol. ++++		Syphilis, late secondary.	Frank case; infected her husband.
29.	Wass. ++++ H. W. ++++	Ale. ++++ Chol. ++++		Syphilis, secondary	No treatment.
30.	Wass. - H. W. -	Ale. - Chol. -		Syphilis, secondary	Received thorough treatment.
31.	Wass. + H. W. +	Ale. - Chol. -		Syphilis, secondary	Frank case of syphilis, secondary stage.
32.	Wass. ++++ H. W. ++++	Ale. - Chol. -		See Case 31.	
33.	Wass. ++++ H. W. ++++	Ale. ++++ Chol. ++++		Tertiary syphilis; double optic neuritis.	Had received insufficient treatment.
34.	Wass. - H. W. -	Ale. - Chol. -		Not syphilitic.	
35.	Wass. - H. W. -	Ale. - Chol. -		Carcinoma chin.	
36.	Wass. ++++ H. W. ++++	Ale. ++++ Chol. ++++		Tertiary syphilis; ulcerated gumma at end of nose.	Wife of a physician; case undiagnosed for one year.
37.	Wass. ++++ H. W. ++++	Ale. ++++ Chol. ++++		Secondary syphilis.	Insufficient treatment.
38.	Wass. - H. W. -	Ale. - Chol. -		Had syphilis.	Thorough treatment.

TABLE I—CONT'D.

CASE NO.	LAB. A	LAB. B	LAB. C	CLINICAL DIAGNOSIS	REMARKS
39.	Wass. — H. W. —	Alc. — Chol. —		Had syphilis.	Thorough treatment.
40.	Wass. +++++ H. W. +++++	Alc. — Chol. —		Tertiary syphilis; ulcerated gumma on penis.	Undiagnosed for six months as Wass. was negative at another laboratory; therapeutic test positive. Lab. B, false negative.
41.	Wass. — H. W. —	Alc. — Chol. —		Carcinoma of rectum.	Roseola present.
42.	Wass. +++++ H. W. +++++	Alc. +++++ Chol. +++++		Secondary syphilis.	Just wanted a Wassermann.
43.	Wass. — H. W. —	Alc. — Chol. —		Not syphilitic.	
44.	Wass. — H. W. —	Alc. — Chol. —		Not syphilitic.	
45.	Wass. — H. W. —	Alc. — Chol. —		Not syphilitic.	
46.	Wass. — H. W. —	Alc. — Chol. —		Carcinoma of the jaw.	
47.	Wass. — H. W. —	Alc. — Chol. —		Tertiary syphilis (tongue).	Both laboratories give false negative.
48.	Wass. +++++ H. W. +++++	Alc. +++++ Chol. +++++		Syphilitic optic neuritis.	Therapeutic test positive.
49.	Wass. — H. W. —	Alc. — Chol. —		Not syphilitic.	Diagnosis confirmed by an oculist. Never treated.
50.	Wass. — H. W. —	Alc. — Chol. —		Not syphilitic.	
51.	Wass. — H. W. —	Alc. — Chol. —		Not syphilitic.	
52.	Wass. — H. W. —	Alc. — Chol. —		Had syphilis.	Thorough treatment.
53.	Wass. +++++ H. W. +++++	Alc. — Chol. —		Tertiary syphilis; ulceration of throat.	Therapeutic test positive. Laboratory B false negative.
54.	Wass. — H. W. —	Alc. — Chol. —		Not syphilitic.	
55.	Wass. — H. W. —	Alc. — Chol. —		Syphilis.	Thorough treatment.
56.	Wass. — H. W. —	Alc. — Chol. —		Tuberculosis of superior maxillary bone.	
57.	Wass. +++++ H. W. +++++	Alc. +++++ Chol. +++++		Tertiary syphilis.	Never diagnosed.
58.	Wass. +++++ H. W. +++++	Alc. +++++ Chol. +++++		Primary syphilis.	Undiagnosed for one month.
59.	Wass. — H. W. —	Alc. — Chol. —		Not syphilitic.	
60.	Wass. — H. W. —	Alc. + Chol. +++++		Cerebrospinal syphilis.	Sept. 24, 1921, Wass. negative; one week later Wass. was still negative. Both Lab. show false negatives.

TABLE I—CONT'D.

CASE NO.	LAB. A	LAB. B	LAB. C	CLINICAL DIAGNOSIS	REMARKS
61.	Wass. + + + + H. W. + + + +	Ale. + + + + Chol. + + + +		Secondary syphilis.	From Sept. 21, 1920, until Feb. 1, 1921, received seven neosalvarsan and eight injections of mercury; Feb. 1, 1921, Wass. negative. Received thorough treatment; Sept. 20, 1920, provocative Wass. negative. Denies exposure.
62.	Wass. - H. W. -	Ale. - Chol. -		Had syphilis.	
63.	Wass. + + + + H. W. + + + +	Ale. + + + + Chol. + + + +		Secondary syphilis.	
64.	Wass. - H. W. -	Ale. - Chol. -		Not syphilitic.	
65.	Wass. - H. W. -	Ale. - Chol. -		Not syphilitic.	
66.	Wass. - H. W. -	Ale. - Chol. -		Pulmonary tuberculosis.	
67.	Wass. - H. W. -	Ale. - Chol. -		Not syphilitic.	
68.	Wass. - H. W. -	Ale. - Chol. -		Not syphilitic.	
69.	Wass. - H. W. -	Ale. - Chol. -		Not syphilitic.	
70.	Wass. - H. W. -	Ale. - Chol. -		Primary syphilis.	Dark field examination positive.
71.	Wass. + + + + H. W. + + + +	Ale. + + + + Chol. + + + +		Secondary syphilis.	Symptoms present.
72.	Wass. - H. W. -	Ale. - Chol. -		Not syphilitic.	
73.	Wass. - H. W. -	Ale. - Chol. -		Tubercular sinus of sternum.	
74.	Wass. + + + + H. W. + + + +	Ale. + + + + Chol. + + + +		Tertiary syphilis.	Syphilitic ulceration of superior maxillary bone undiagnosed for one year. Had been under treatment for a year and a half.
75.	Wass. + + + + H. W. + + + +	Ale. + + + + Chol. + + + +		Late secondary syphilis.	Palmar syphilide; began treatment Oct. 4, 1919. Wass. 4-plus; received twenty-seven injections mercury and five injections old salvarsan; Aug. 14, 1920 Wass. was negative.
76.	Wass. - H. W. -	Ale. - Chol. -		Tertiary syphilis.	All clinical symptoms present; Mar. 30, 1920, Wass. positive; received 8 injections of mercury and 5 injections of old salvarsan Oct. 4, 1920, Wass. negative.
77.	Wass. - H. W. -	Ale. - Chol. -		Secondary syphilis.	Lab. C gives false positive.
78.	Wass. - H. W. -	Ale. - Chol. -		Not syphilitic.	Treated three years.
79.	Wass. - H. W. -	Ale. - Chol. -		Had syphilis.	Later become strongly positive.

TABLE I—CONT'D.

CASE NO.	LAB. A	LAB. B	LAB. C	CLINICAL DIAGNOSIS	REMARKS
80.	Wass. + + + + + H. W. + + + + +	Alc. + Chol. + + + + +	Alc. + + Chol. + + + + +	Tertiary syphilis of scalp.	Denies infection; never treated.
81.	Wass. - H. W. -	Alc. - Chol. -	Alc. - Chol. -	Syphilophobia.	
82.	Wass. - H. W. -	Alc. - Chol. -	Alc. - Chol. -	Not syphilitic.	
83.	Wass. - H. W. -	Alc. - Chol. -	Alc. - Chol. -	Not syphilitic.	
84.	Wass. - H. W. -	Alc. - Chol. -	Alc. - Chol. -	Had syphilis.	Four years' thorough treatment.
85.	Wass. - H. W. -	Alc. - Chol. -	Alc. - Chol. -	Had syphilis.	Thorough treatment.
86.	Wass. - H. W. -	Alc. - Chol. -	Alc. - Chol. -	Epithelioma of arm.	
87.	Wass. + + H. W. + + + + +	Alc. - Chol. + + + + +	Alc. - Chol. + + + + +	Tertiary syphilis.	No treatment. Lab. B and C false negative.
88.	Wass. + + + + + H. W. + + + + +	Alc. + + + + + Chol. + + + + +	Alc. + + + + + Chol. + + + + +	Secondary syphilis.	Rosacea present.
89.	Wass. + + + + + H. W. + + + + +	Alc. + + + + + Chol. + + + + +	Alc. + + + + + Chol. + + + + +	Tertiary syphilis.	Symptoms present.
90.	Wass. - H. W. -	Alc. - Chol. -	Alc. + + + + + Chol. + + + + +	Syphilis.	Under treatment. Wass. no guide here to treatment.
91.	Wass. - H. W. -	Alc. - Chol. -	Alc. + + Chol. + +	Tertiary syphilis.	Under treatment.
92.	Wass. - H. W. -	Alc. - Chol. -	Alc. - Chol. -	Not syphilitic.	
93.	Wass. - H. W. -	Alc. - Chol. -	Alc. + + + + + Chol. + + + + +	Psoriasis.	Lab. C false positive.
94.	Wass. - H. W. -	Alc. - Chol. -	Alc. - Chol. -	Not syphilitic.	Observe false positive, Chol. antigen.
95.	Wass. - H. W. -	Alc. - Chol. -	Alc. - Chol. -	Secondary syphilis.	Treated only with salvarsan, once every two weeks; negative after four injections of old salvarsan; remained negative up-to-date.
96.	Wass. - H. W. -	Alc. + Chol. -	Alc. + + + + + Chol. + + + + +	Secondary syphilis.	Thorough treatment. Lab. C give false positive.
97.	Wass. - H. W. -	Alc. - Chol. -	Alc. - Chol. -	Inherited syphilitic leg ulcer.	Therapeutic test positive.
98.	Wass. - H. W. -	Alc. - Chol. -	Alc. - Chol. -	Had syphilis.	Thorough treatment. Lab. C gives false positive. Later Wass. negative to 3 laboratories without further treatment.
99.	Wass. - H. W. -	Alc. - Chol. -	Alc. - Chol. -	Not syphilitic.	
100.	Wass. - H. W. + + + + +	Alc. - Chol. -	Alc. - Chol. -	Not syphilitic.	False positive H. W. and Chol.

TABLE I—CONT'D.

CASE NO.	LAB. A	LAB. B	LAB. C	CLINICAL DIAGNOSIS	REMARKS
101.	Wass. +	Ale. -	Ale. -	Carcinoma of uterus.	
102.	H. W. -	Chol. -	Chol. -	Not syphilitic.	False positive chol.
103.	Wass. -	Chol. +	Chol. -	Not syphilitic.	
104.	H. W. -	Chol. -	Chol. -	Not syphilitic.	
105.	Wass. -	Ale. -	Ale. + + + +	Undetermined case of syphilis.	Same as Case 21. Observe the continued variation in Wass. in this case.
106.	H. W. -	Ale. -	Chol. + + + +	Lichen planus of mouth.	No history, no symptoms. Lab. C false positive.
107.	Wass. -	Chol. -	Chol. -	Not syphilitic.	
108.	H. W. -	Chol. -	Chol. -	Syphilophobia.	Lab. C false positive.
109.	Wass. -	Ale. -	Ale. + +	Not syphilitic.	
110.	H. W. -	Chol. -	Ale. + + + + +	Cerebrospinal syphilis.	Optic changes confirmed by oculist. Lab. A and B false negative.
111.	Wass. -	Chol. -	Chol. -	Syphilis.	Three years' duration; under treatment. Lab. B and C false pos. Chol. antigen. Treated before Wass. was positive.
112.	H. W. -	Chol. -	Chol. -	Had syphilis.	Insufficiently treated.
113.	Wass. -	Ale. -	Ale. + + + +	Tertiary syphilis.	Same as Case 31.
114.	H. W. -	Chol. -	Chol. -	Syphilis.	Symptoms present.
115.	Wass. -	Ale. -	Ale. + + + + +	Secondary syphilis.	Thorough treatment.
116.	H. W. -	Chol. -	Chol. -	Had syphilis.	
117.	Wass. -	Ale. -	Ale. -	Raynaud's disease.	
118.	H. W. -	Chol. -	Chol. -	Not syphilitic.	
119.	Wass. +	Chol. -	Chol. -	Tertiary syphilis.	Paralysis of left external rectus muscle. (Oculist report.) Infected 12 years ago. Lab. A false neg.
120.	H. W. -	Ale. -	Ale. + + + +	Tertiary syphilis.	Palmer syphilis, insufficiently treated. Lab. A and B false neg.
121.	Wass. -	Chol. -	Chol. -	Psoriasis.	
122.	H. W. -	Chol. -	Chol. -	Syphilis, palmar.	Under treatment. Lab. C false positive.
	Wass. + + + +	Chol. + + + +	Chol. + + + +	Syphilis.	Initial lesion of left tonsil, infected by husband.

TABLE I—CONT'D.

CASE NO.	LAB. A	LAB. B	LAB. C	CLINICAL DIAGNOSIS	REMARKS
123.	Wass. - H. W. -	Alc. - Chol. +	Alc. - Chol. +	Syphilophobia.	
124.	Wass. - H. W. -	Alc. - Chol. +	Alc. - Chol. +	Not syphilitic.	
125.	Wass. - H. W. -	Alc. - Chol. -	Alc. - Chol. -	Tubercular adenitis.	
126.	Wass. +++++ H. W. +++++	Alc. - Chol. +++++	Alc. ++ Chol. ++	Tabes.	Physician, indefinite history; infected about 30 years ago; never treated. Lab. B. false negative.
127.	Wass. - H. W. -	Alc. - Chol. -	Alc. - Chol. -	Not syphilitic.	Thorough treatment.
128.	Wass. - H. W. -	Alc. - Chol. -	Alc. - Chol. -	Had syphilis.	Under treatment. Lab. A and B false negative. Later three laboratories reported four-plus while taking treatment.
129.	Wass. - H. W. ++	Alc. - Chol. +++++	Alc. +++++ Chol. +++++	Syphilis.	Large squamous patches on palms and body; undiagnosed for 12 years. Lab. B, false negative. Lab. A and C false negative. Clinical symptoms present.
130.	Wass. +++++ H. W. +++++	Alc. - Chol. +++++	Alc. +++++ Chol. +++++	Tertiary syphilis.	Infiltration of right cheek; undiagnosed for one year thought to be malignant; therapeutic test positive.
131.	Wass. - H. W. ++	Alc. ++ Chol. +++++	Alc. - Chol. -	Tabes.	Lab. C, false positive.
132.	Wass. - H. W. -	Alc. - Chol. -	Alc. - Chol. -	Not syphilitic.	Palmar syphilis; positive history.
133.	Wass. +++++ H. W. +++++	Alc. +++++ Chol. +++++	Alc. +++++ Chol. +++++	Tertiary syphilis.	Lab. C, false positive.
134.	Wass. - H. W. -	Alc. - Chol. -	Alc. - Chol. -	Feigned eruption on arm.	Lab. C, false positive.
135.	Wass. - H. W. -	Alc. - Chol. -	Alc. ++ Chol. ++	Not syphilis.	Palmar syphilis; positive history.
136.	Wass. ++ H. W. +++++	Alc. - Chol. -	Alc. ++ Chol. +++++	Tertiary syphilis.	Lab. C, false positive.
137.	Wass. - H. W. -	Alc. - Chol. ++	Alc. ++ Chol. ++	Not syphilitic.	Lab. C, false positive.
138.	Wass. - H. W. -	Alc. - Chol. -	Alc. ++ Chol. ++	Not syphilitic.	Lab. C, false positive.
139.	Wass. - H. W. ++	Alc. - Chol. -	Alc. ++ Chol. ++	Syphilis.	Sixth year still under treatment. Lab. C, false positive.
140.	Wass. +++++ H. W. +++++	Alc. - Chol. +++++	Alc. - Chol. -	Syphilis.	Fourth year under treatment. Case later while still under treatment became positive.
141.	Wass. - H. W. +++++	Alc. - Chol. +++++	Alc. ++ Chol. +++++	Syphilis.	Second year under treatment. Lab. C, false positive.
142.	Wass. - H. W. -	Alc. - Chol. -	Alc. - Chol. -	Psoriasis.	
143.	Wass. - H. W. -	Alc. - Chol. -	Alc. - Chol. -	Not syphilitic.	

TABLE I—Cont'd.

CASE NO.	LAB.			LAB.		CLINICAL DIAGNOSIS	REMARKS
	A	B	C	O	+		
144.	Wass. + + + + H. W. + + + +	Ale. — Chol. —	Ale. + + Chol. + + +	+	+	Primary syphilis.	Dark-field examination positive.
145.	Wass. — H. W. —	Ale. — Chol. —	Ale. — Chol. —	—	—	Not syphilis.	
146.	Wass. — H. W. —	Ale. — Chol. —	Ale. — Chol. —	—	—	Not syphilis.	
147.	Wass. + + + + H. W. + + + +	Ale. + + + + Chol. + + + +	Ale. + + + + Chol. + + + +	+	+	Early secondary syphilis.	Symptoms present.
148.	Wass. — H. W. —	Ale. — Chol. —	Ale. — Chol. —	—	—	Not syphilitic.	
149.	Wass. — H. W. —	Ale. — Chol. —	Ale. — Chol. —	+	+	Treated syphilis.	Lab. C, false positive.
150.	Wass. — H. W. —	Ale. — Chol. —	Ale. — Chol. —	+	+	Syphilis.	Second year; had thorough treatment.
151.	Wass. + + + + H. W. + + + +	Ale. + + + + Chol. + + + +	Ale. + + + + Chol. + + + +	+	+	Primary syphilis.	Six months under treatment.
152.	Wass. — H. W. —	Ale. — Chol. —	Ale. — Chol. —	—	—	Not syphilitic.	
153.	Wass. — H. W. —	Ale. — Chol. —	Ale. — Chol. —	+	+	Not syphilitic.	Traumatic leg ulcer.
154.	Wass. — H. W. —	Ale. — Chol. —	Ale. — Chol. —	+	+	Syphilis.	Third year, thorough treatment.
155.	Wass. + + + + H. W. + + + +	Ale. + + + + Chol. + + + +	Ale. + + + + Chol. + + + +	+	+	Syphilis.	Third stage; multiple gumma of legs and abdomen.
156.	Wass. + + + + H. W. + + + +	Ale. + + + + Chol. + + + +	Ale. + + + + Chol. + + + +	+	+	Primary syphilis.	Symptoms present.
157.	Wass. — H. W. —	Ale. — Chol. —	Ale. — Chol. —	+	+	Syphilis.	Thorough treatment.
158.	Wass. + + + + H. W. + + + +	Ale. — Chol. —	Ale. + + + + Chol. + + + +	+	+	Syphilis.	Three years' duration; no symptoms; never diagnosed.
159.	Wass. + + + + H. W. + + + +	Ale. + + + + Chol. + + + +	Ale. + + + + Chol. + + + +	+	+	Syphilis.	Optic neuritis, confirmed by oculist.
160.	Wass. + + + + H. W. + + + +	Ale. — Chol. —	Ale. + + + + Chol. + + + +	+	+	Tertiary Syphilis.	Had been under treatment for three years; involvement of the auditory nerve.
161.	Wass. + + + + H. W. + + + +	Ale. + + + + Chol. + + + +	Ale. + + + + Chol. + + + +	+	+	Tertiary Syphilis.	Gumma of left arm; denies infection; refused to be treated after lesions healed.
162.	Wass. — H. W. —	Ale. — Chol. —	Ale. — Chol. —	—	—	Secondary syphilis.	Sept. 12, 1920, to Dec. 31, 1920, received seven neosalvarsan injections, dose 0.9 and eight injections of mercury; Feb. 1, 1921, Wass. negative. See Case 21.
163.	Wass. + + + + H. W. + + + +	Ale. — Chol. —	Ale. + + + + Chol. + + + +	+	+	Undetermined case of syphilis.	30 years' duration.
164.	Wass. — H. W. —	Ale. — Chol. —	Ale. — Chol. —	+	+	Epithelioma on abdominal wall.	
165.	Wass. + + + + H. W. + + + +	Ale. + + + + Chol. + + + +	Ale. + + + + Chol. + + + +	+	+	Syphilis.	Three years' duration; treated insufficiently.

TABLE I—Cont'd.

CASE NO.	LAB. A	LAB. B	LAB. C	CLINICAL DIAGNOSIS	REMARKS
166.	Wass. ++ H. W. + + + +	Alc. - Chol. -	Alc. + + + + Chol. + + + +	Syphilis.	See Case 158; impossible to get a positive Wass. from Lab. B in this case.
167.	Wass. - H. W. -	Alc. - Chol. -	Alc. - Chol. -	Not syphilitic.	
168.	Wass. - H. W. -	Alc. - Chol. -	Alc. - Chol. -	Not syphilitic.	
169.	Wass. - H. W. -	Alc. - Chol. -	Alc. - Chol. -	Tubercule of lower limbs.	Tubercular adenitis.
170.	Wass. Anticom- plementary	Alc. - Chol. -	Alc. + + Chol. + + + +	Undetermined case of syphilis	See Case 21.
171.	H. W. - Wass. -	Alc. - Chol. -	Alc. - Chol. -	Not syphilitic.	
172.	H. W. - Wass. -	Alc. - Chol. -	Alc. - Chol. -	Parasitic eczema of the thighs.	
173.	H. W. - Wass. -	Alc. - Chol. -	Alc. - Chol. -	Syphilis.	Four-plus two years ago; now negative without treatment for one year. See Case 21.
174.	H. W. - Wass. -	Alc. - Chol. -	Alc. + + Chol. + +	Undetermined case.	
175.	H. W. - Wass. -	Alc. - Chol. -	Alc. - Chol. -	Not syphilitic.	
176.	H. W. + + + + Wass. + + + +	Alc. + + + + Chol. + + + +	Alc. + + + + Chol. + + + +	Primary and secondary syphilis.	All symptoms present.
177.	H. W. - Wass. -	Alc. - Chol. -	Alc. - Chol. -	Treated syphilis.	History shows that this man was infected twice.
178.	H. W. - Wass. -	Alc. - Chol. -	Alc. - Chol. -	Neurosyphilis.	History of syphilis; evidence of neurosyphilis confirmed by neurologist.
179.	H. W. - Wass. -	Alc. - Chol. -	Alc. - Chol. -	Not syphilitic.	
180.	H. W. + + + + Wass. + + + +	Alc. - Chol. -	Alc. - Chol. -	Treated syphilis.	Two years' duration; persistent treatment; Wass. stands out to be distinctly negative in this case.
181.	Wass. + + H. W. + + + +	Alc. - Chol. -	Alc. + + + + Chol. + + + +	Tertiary syphilis.	Ulcerated gumma of tip of tongue diagnosed as epithelioma; therapeutic test positive.
182.	Wass. - H. W. -	Alc. - Chol. -	Alc. - Chol. -	Not syphilitic.	
183.	Wass. - H. W. -	Alc. - Chol. -	Alc. - Chol. -	Epithelioma of lower lip.	
184.	Wass. + + + + H. W. + + + +	Alc. + + + + Chol. + + + +	Alc. + + + + Chol. + + + +	Secondary syphilis.	Man she was infected by is Case 188.
185.	Wass. - H. W. -	Alc. - Chol. -	Alc. - Chol. -	Not syphilitic.	
186.	Wass. - H. W. -	Alc. - Chol. -	Alc. - Chol. -	Not syphilitic.	
187.	Wass. - H. W. -	Alc. - Chol. -	Alc. - Chol. -	Not syphilitic.	



TABLE I—CONT'D.

CASE NO.	LAB. A	LAB. B	LAB. C	CLINICAL DIAGNOSIS	REMARKS
188.	Wass. + H. W. + + + +	Alc. - Chol. -	Alc. - Chol. -	Syphilis.	Infected two years ago. No treatment; was able to prove that he infected patient 184. Lab. reports all negative. While under treatment two became positive. See Case 198. Primary chancre of lip eight years ago; received very little treatment; see Case 196.
189.	Wass. - H. W. -	Alc. - Chol. -	Alc. - Chol. -	Treated syphilis.	Husband to Case 189; no evidence of infection.
190.	Wass. - H. W. -	Alc. - Chol. -	Alc. - Chol. -	Not syphilitic.	
191.	Wass. - H. W. -	Alc. - Chol. -	Alc. - Chol. -	Acne rosacea.	
192.	Wass. - H. W. -	Alc. - Chol. -	Alc. - Chol. -	Not syphilitic.	
193.	Wass. - H. W. -	Alc. - Chol. -	Alc. - Chol. -	Not syphilitic.	
194.	Wass. + + + + H. W. + + + +	Alc. - Chol. -	Alc. + + + + Chol. + + + +	Paresis.	12 years' duration; diagnosis confirmed by neurologist.
195.	Wass. - H. W. -	Alc. - Chol. -	Alc. - Chol. -	See Case 189.	
196.	Wass. - H. W. -	Alc. - Chol. -	Alc. - Chol. -	Not syphilitic.	
197.	Wass. - H. W. -	Alc. - Chol. -	Alc. - Chol. -	Not syphilitic.	
198.	Wass. + + H. W. + + + +	Alc. - Chol. -	Alc. + + + + Chol. + + + +	Provocative test on Case 188, shows Lab.C. is now strongly positive; patient refused further treatment. But Lab. B continues negative. Epithelioma of urethra.	
199.	Wass. - H. W. -	Alc. - Chol. -	Alc. - Chol. -	Treated syphilis.	Frank case of syphilis four years ago; today shows a distinct peritonsitis on right side of nose, small subcutaneous gumma under left jaw; therapeutic test positive.
200.	Wass. - H. W. -	Alc. - Chol. -	Alc. - Chol. -		
201.	Wass. - H. W. -	Alc. - Chol. -	Alc. - Chol. -	Epithelioma of the lip.	
202.	Wass. - H. W. -	Alc. - Chol. -	Alc. - Chol. -	Not syphilitic.	
203.	Wass. - H. W. -	Alc. - Chol. -	Alc. - Chol. -	Not syphilitic.	
204.	Wass. - H. W. -	Alc. - Chol. -	Alc. - Chol. -	Not syphilitic.	
205.	Wass. - H. W. + + + +	Alc. + + + + Chol. + + + +	Alc. + + + + Chol. + + + +	Syphilis and carcinoma of vulva.	Treated six months without correct diagnosis. Lab. A, false.
206.	Wass. - H. W. -	Alc. - Chol. -	Alc. - Chol. -	Treated syphilis.	Wife positive case of syphilis.

TABLE I—Cont'd.

CASE NO.	LAB. A	LAB. B	LAB. C	CLINICAL DIAGNOSIS	REMARKS
207.	Wass. — H. W. —	Alc. — Chol. + + + +	Alc. — Chol. —	Treated syphilis.	See Case 4.
208.	Wass. — H. W. —	Alc. — Chol. —	Alc. — Chol. —	Not syphilitic.	
209.	Wass. + + + + H. W. + + + +	Alc. + + + + Chol. + + + +	Alc. + + + + Chol. + + + +	Syphilitic iritis.	Was told Wass. was negative two months previous.
210.	Wass. — H. W. —	Alc. — Chol. —	Alc. — Chol. —	Not syphilitic.	
211.	Wass. — H. W. —	Alc. — Chol. —	Alc. — Chol. —	Not syphilitic.	
212.	Wass. — H. W. —	Alc. — Chol. + + + +	Alc. — Chol. —	Treated syphilis.	Husband was negative.
213.	Wass. Anticom- plementary H. W. —	Alc. — Chol. + + + +	Alc. — Chol. + + + +	Treated syphilis.	See Case 31.
214.	Wass. + + + + H. W. + + + +	Alc. — Chol. + + + +	Alc. — Chol. + + + +	Tubercule of lower limbs.	No history of syphilis; had been a patient of mine for the last eight years.
215.	Wass. Anticom- plementary H. W. —	Alc. + + + + Chol. + + + +	Alc. + + + + Chol. + + + +	Tertiary syphilis.	Small ulcerated gumma of the side of the nose and eyelid; no history of infection; wife's Wass. negative, mother of one healthy child.
216.	Wass. — H. W. —	Alc. — Chol. + +	Alc. — Chol. + +	Not syphilitic.	Three weeks' duration; dark-field examination positive, Lab. B false negative.
217.	Wass. + + + + H. W. + + + +	Alc. — Chol. + +	Alc. — Chol. + + + +	Primary syphilis.	See Case 31-213. Lab. B false negative.
218.	Wass. + + + + H. W. + + + +	Alc. — Chol. + + + +	Alc. + + + + Chol. + + + +	Treated syphilis.	Husband's Wass. positive and known case of syphilis; dark-field examination positive. Later Wass. became positive.
219.	Wass. — H. W. —	Alc. — Chol. —	Alc. — Chol. —	Treated syphilis.	
220.	Wass. — H. W. —	Alc. — Chol. —	Alc. — Chol. —	Primary syphilis.	
221.	Wass. — H. W. —	Alc. — Chol. —	Alc. — Chol. —	Not syphilitic.	Lab. A-false positive; see Case 214.
222.	Wass. + + + + H. W. + + + +	Alc. — Chol. + + + +	Alc. — Chol. + +	Not syphilitic.	
223.	Wass. — H. W. —	Alc. — Chol. —	Alc. — Chol. —	Not syphilitic.	
224.	Wass. + + + + H. W. + + + +	Alc. — Chol. —	Alc. — Chol. —	Not syphilitic.	Fourth Laboratory report, Wass. four- plus. See Cases 213, 31, 218.
225.	Wass. — H. W. —	Alc. — Chol. —	Alc. — Chol. —	Not syphilitic.	Mother of a healthy child; no evi- dence of syphilis; husband, Case 215.
226.	Wass. + + + + H. W. + + + +	Alc. — Chol. —	Alc. + + + + Chol. + + + +	Tertiary syphilis.	Husband of Case 225; see also Case 215, Lab. B false negative.
227.	Wass. — H. W. —	Alc. — Chol. —	Alc. — Chol. —	Tubercular adenitis.	

TABLE I—CONT'D.

CASE NO.	LAB. A	LAB. B	LAB. C	CLINICAL DIAGNOSIS	REMARKS
228.	Wass. + H. W. + + + + +	Ale. - Chol. -	Ale. - Chol. -	Not syphilitic.	No history or clinical evidence. Lab. A, false H. W. Never knew he had syphilis until he was informed wife was four-plus.
229.	Wass. + + + + + H. W. + + + + +	Ale. + + + + + Chol. + + + + +	Ale. + + + + + Chol. + + + + +	Syphilis.	
230.	Wass. - H. W. -	Ale. - Chol. -	Ale. - Chol. -	Lupus erythematosus of nose.	
231.	Wass. + + + + + H. W. + + + + +	Ale. - Chol. -	Ale. - Chol. -	Syphilis.	History and clinical evidence positive; Lab. B and C, false negative.
232.	Wass. + + + + + H. W. + + + + +	Ale. - Chol. -	Ale. - Chol. -	Syphilitic rheumatism?	History and clinical evidence doubtful. Therapeutic test negative. Lab. A false positive.
233.	Wass. + + + + + H. W. + + + + +	Ale. + + + + + Chol. + + + + +	Ale. + + + + + Chol. + + + + +	Treated syphilis.	Three years' duration.
234.	Wass. - H. W. -	Ale. - Chol. -	Ale. - Chol. -	Not syphilis.	
235.	Wass. - H. W. -	Ale. - Chol. -	Ale. - Chol. -	Not syphilis.	
236.	Wass. + + H. W. + + + + +	Ale. - Chol. + + +	Ale. - Chol. + + +	Treated syphilis.	Three years' duration; eight injections of salvarsan once a month. No mercury. Lab. B false negative. Wife Case 206 persistently negative.
237.	Wass. + + + + + H. W. + + + + +	Ale. + + + + + Chol. + + + + +	Ale. + + + + + Chol. + + + + +	Syphilis.	Two years' duration; syphilitic ulceration of septum nasi. Not diagnosed. No history or clinical evidence of syphilis.
238.	Wass. - H. W. -	Ale. - Chol. -	Ale. - Chol. -	Iritis.	Symptoms present 12 years; Lab. B false negatives.
239.	Wass. + + + + +	Ale. -	Ale. + + + + +	Tabs.	20 years' duration, inefficient treatment. Lab. B, false neg.
240.	Wass. + + + + + H. W. + + + + +	Ale. - Chol. -	Ale. + + + + + Chol. + + + + +	Syphilis.	Six months' duration, intense treatment. Case 90. This case I consider positive although Lab. B is negative.
241.	Wass. - H. W. -	Ale. - Chol. + +	Ale. - Chol. -	Syphilis.	Four years' duration, distinct history, no symptoms, syphilitic orchitis. Lab. A and B, false negative.
242.	Wass. + + + + + H. W. + + + + +	Ale. - Chol. -	Ale. + + + + + Chol. + + + + +	Tertiary syphilis.	
243.	Wass. - H. W. Sus. Pos.	Ale. - Chol. + + + + +	Ale. - Chol. + + + + +	Tertiary syphilis.	
244.	Wass. - H. W. -	Ale. - Chol. -	Ale. - Chol. -	Melanotic sarcoma of cornea.	
245.	Wass. - H. W. -	Ale. - Chol. -	Ale. - Chol. -	Not syphilitic.	
246.	Wass. - H. W. -	Ale. - Chol. + +	Ale. - Chol. -	Not syphilitic.	Wife is Case 247. False positive Chol. antigen.
247.	Wass. + + + + + H. W. -	Ale. + + + + + Chol. + + + + +	Ale. + + + + + Chol. + + + + +	Tertiary syphilis.	Ulcerated syphilitic gumma of the pharynx involving the soft palate; no history of infection, mother of two healthy children treated six months without diagnosis being made; wife of Case 246. Lab. A, false negative.

TABLE I—CONT'D.

CASE NO.	LAB. A	LAB. B	LAB. C	CLINICAL DIAGNOSIS	REMARKS
248.	Wass. - H. W. -	Alc. - Chol. -	Alc. - Chol. -	Rodent ulcer, of right mastoid region.	
249.	Wass. - H. W. -	Alc. - Chol. -	Alc. - Chol. -	Not syphilitic.	
250.	Wass. - H. W. -	Alc. - Chol. -	Alc. - Chol. -	Tertiary syphilis.	Therapeutic test positive.
251.	Wass. + + + + H. W. + + + +	Alc. + + Chol. + + + +	Alc. + + + + Chol. + + + +	Paresis.	See Case 194.
252.	Wass. - H. W. -	Alc. - Chol. -	Alc. - Chol. -	Not syphilitic.	
253.	Wass. - H. W. -	Alc. - Chol. -	Alc. - Chol. -	Syphilis treated five years.	Not treated for three years.
254.	Wass. - H. W. -	Alc. - Chol. -	Alc. - Chol. -	Syphilis five years.	Not treated for three years. Husband of Case 253.
255.	Wass. - H. W. -	Alc. - Chol. -	Alc. - Chol. -	Psoriasis.	
256.	Wass. - H. W. -	Alc. - Chol. -	Alc. - Chol. -	Syphilis.	Treated for six months.
257.	Wass. - H. W. -	Alc. - Chol. -	Alc. - Chol. -	Lichen Planus.	No clinical signs or history.
258.	Wass. - H. W. -	Alc. - Chol. -	Alc. - Chol. -	Treated syphilis.	Cholesterinized antigen false positive.
259.	Wass. - H. W. -	Alc. - Chol. -	Alc. - Chol. -	Tertiary syphilis.	Multiple gumma both legs, known syphilitic patient. False Wassermann report.
260.	Wass. + + H. W. + + + +	Alc. - Chol. -	Alc. + + + + Chol. + + + +	Syphilis.	Two years' duration. Positive history of syphilis.
261.	Wass. + + + + H. W. + + + +	Alc. - Chol. +	Alc. + + + + Chol. + + + +	Gumma and carcinoma lower lip.	Histologic report gumma. No history of syphilis, antisyphilitic treatment produced negative Wassermann. Lip, however, continued to grow worse with secondary glandular involvement. Intense radium treatment checked the process.
262.	Wass. - H. W. -	Alc. - Chol. -	Alc. - Chol. -	Syphilis.	Treated 12 years ago.
263.	Wass. + + + + H. W. + + + +	Alc. + + + + Chol. + + + +	Alc. + + + + Chol. + + + +	Mass at pyloric end of stomach, probably malignant, strong clinical evidence of syphilis, patient probably has both conditions.	
264.	Wass. - H. W. -	Alc. - Chol. -	Alc. - Chol. -	Beginning tabs.	
265.	Wass. - H. W. -	Alc. - Chol. -	Alc. - Chol. -	Not syphilitic.	Wife has tabs. See Case 131. Diagnosis confirmed by a neurologist.
266.	Wass. - H. W. -	Alc. - Chol. -	Alc. - Chol. -	Treated syphilis.	See Case 31.

TABLE I—CONT'D.

CASE NO.	LAB. A	LAB. B	LAB. C	CLINICAL DIAGNOSIS	REMARKS
267.	Wass. — H. W. —	Ale. — Chol. —	Ale. — Chol. —	Treated syphilis.	Man under treatment for five years.
268.	Wass. — H. W. —	Ale. — Chol. —	Ale. — Chol. —	Not syphilitic.	Abdominal tumor.
269.	Wass. — H. W. +	Ale. — Chol. —	Ale. + + + + Chol. —	Treated syphilis.	Provocative test of Case 266.
270.	Wass. — H. W. —	Ale. — Chol. —	Ale. — Chol. —	Not syphilitic.	
271.	Wass. — H. W. —	Ale. — Chol. —	Ale. — Chol. —	Carcinoma urethra.	
272.	Wass. — H. W. —	Ale. — Chol. —	Ale. — Chol. —	Syphilis.	Thorough treatment.
273.	Wass. — H. W. —	Ale. — Chol. —	Ale. — Chol. —	Tabs.	Provocative of Case 264.
274.	Wass. — H. W. —	Ale. — Chol. —	Ale. — Chol. —	Not syphilitic.	Gonorrheal rheumatism.
275.	Wass. — H. W. —	Ale. — Chol. —	Ale. — Chol. —	Treated syphilis.	
276.	Wass. — H. W. —	Ale. — Chol. —	Ale. — Chol. —	Keratosis fingers.	
277.	Wass. + + + + H. W. + + + +	Ale. + + Chol. + + + +	Ale. + + + + Chol. + + + +	Tertiary syphilis. Optic atrophy.	No history of infection, never treated.
278.	Wass. + + + + H. W. + + + +	Ale. + + + + Chol. + + + +	Ale. + + + + Chol. + + + +	Late secondary papular syphilide of the face.	This Wassermann was reported negative to patient when he was confined to a hospital in Penmayivania.
279.	Wass. — H. W. —	Ale. — Chol. —	Ale. — Chol. —	Not syphilitic.	
280.	Wass. + + + + H. W. + + + +	Ale. — Chol. —	Ale. + + + + Chol. + + + +	Secondary syphilis four months' duration.	Infected by her husband. No symptoms.
281.	Wass. + + + + H. W. + + + +	Ale. + + + + Chol. + + + +	Ale. + + + + Chol. + + + +	Tertiary syphilis.	Three years' duration. Multiple gumma penis.
282.	Wass. + + H. W. + + + +	Ale. + + Chol. —	Ale. + + Chol. + + + +	Tertiary syphilis.	Same as Case 261. After three salvarsans and 3 mercury injections, since his first Wassermann three months ago.
283.	Wass. + + + + H. W. + + + +	Ale. — Chol. —	Ale. + + + + Chol. + + + +	Tertiary syphilis.	Evidently Lab. B is at fault as this is a known case of syphilis.
284.	Wass. — H. W. —	Ale. — Chol. —	Ale. — Chol. —	Treated case of syphilis.	
285.	Wass. — H. W. —	Ale. — Chol. —	Ale. — Chol. —	Syphilis.	This patient was well treated clinically.
286.	Wass. — H. W. —	Ale. — Chol. —	Ale. — Chol. —	Treated case of syphilis.	Received thorough treatment.
287.	Wass. + + + + H. W. + + + +	Ale. + + + + Chol. + + + +	Ale. + + + + Chol. + + + +	Frank case of secondary syphilis.	All symptoms present.
288.	Wass. — H. W. —	Ale. — Chol. —	Ale. — Chol. —	Not syphilitic.	

TABLE I—CONT'D.

CASE NO.	LAB. A	LAB. B	LAB. C	CLINICAL DIAGNOSIS	REMARKS
289.	Wass. — H. W. Sus. Pos.	Alc. — Chol. —	Alc. — Chol. —	Treated case of syphilis.	
290.	Wass. — H. W. —	Alc. — Chol. —	Alc. — Chol. —	Treated case of syphilis.	
291.	Wass. + + + + H. W. + + + +	Alc. — Chol. + + + +	Alc. + + + + Chol. + + + +	Syphilis.	Specific ulceration tongue.
292.	Wass. — H. W. —	Alc. — Chol. —	Alc. — Chol. —	Syphilis.	Received thorough treatment.
293.	Wass. — H. W. —	Alc. — Chol. —	Alc. — Chol. —	Not syphilitic.	
294.	Wass. — H. W. —	Alc. — Chol. —	Alc. — Chol. —	Primary syphilis.	
295.	Wass. — H. W. —	Alc. — Chol. —	Alc. — Chol. —	Not syphilis.	Under treatment. No clinical symptoms present.
296.	Wass. — H. W. —	Alc. — Chol. —	Alc. — Chol. —	Syphilitic infection three years ago.	Well treated.
297.	Wass. + + + + H. W. + + + +	Alc. + + + + Chol. + + + +	Alc. + + + + Chol. + + + +	Syphilis.	Wife of Case 282.
298.	Wass. — H. W. —	Alc. — Chol. —	Alc. — Chol. —	Not syphilis.	
299.	Wass. — H. W. —	Alc. — Chol. —	Alc. — Chol. —	Treated case of syphilis.	
300.	Wass. + + + + H. W. + + + +	Alc. + + + + Chol. + + + +	Alc. + + + + Chol. + + + +	Tertiary syphilis.	Positive history. No symptoms.
301.	Wass. — H. W. —	Alc. — Chol. —	Alc. — Chol. —	Chancroidal infection.	
302.	Wass. — H. W. —	Alc. — Chol. —	Alc. — Chol. —	Treated syphilis.	
303.	Wass. — H. W. —	Alc. — Chol. —	Alc. — Chol. —	Chancroidal Infection.	
304.	Wass. — H. W. —	Alc. — Chol. —	Alc. — Chol. —	Treated syphilis.	
305.	Wass. — H. W. —	Alc. — Chol. —	Alc. — Chol. —	Not syphilitic.	
306.	Wass. — H. W. —	Alc. — Chol. —	Alc. — Chol. —	Not syphilitic.	
307.	Wass. — H. W. —	Alc. — Chol. —	Alc. — Chol. —	Treated syphilis.	
308.	Wass. — H. W. —	Alc. — Chol. —	Alc. — Chol. —	Huntarian chancre present.	Wassermann not yet positive. See Case 315.
309.	Wass. — H. W. —	Alc. — Chol. —	Alc. — Chol. —	Syphilis and cancer of lip.	See Case 282.
310.	Wass. + + + + H. W. + + + +	Alc. + + + + Chol. + + + +	Alc. + + + + Chol. + + + +	Cerebrospinal syphilis.	
311.	Wass. — H. W. —	Alc. — Chol. —	Alc. — Chol. —	Syphilis.	Thoroughly treated.
312.	Wass. — H. W. —	Alc. — Chol. —	Alc. — Chol. —	Lichen planus hypertrophicus.	

TABLE I—CONT'D.

CASE NO.	LAB. A	LAB. B	LAB. C	CLINICAL DIAGNOSIS	REMARKS
313.	Wass. — H. W. —	Alc. — Chol. —	Alc. — Chol. —	Syphilitic leg ulcer.	Wassermann persistently negative, therapeutic test positive.
314.	Wass. + + + + + H. W. + + + + +	Alc. + + + Chol. + + +	Alc. + + + + + Chol. + + + + +	Frank case secondary syphilis.	Mucous patches of the external genitalia.
315.	Wass. + + + + + H. W. + + + + +	Alc. — Chol. + + +	Alc. + + + + + Chol. + + + + +	Primary stage of syphilis.	First time patient presented himself since first Wassermann. See Case 308.
316.	Wass. — H. W. —	Alc. — Chol. —	Alc. — Chol. —	Syphilis thoroughly treated.	Dec., 1918, patient had a frank case of secondary syphilis, Wassermann was 4-plus. After 4 injections of neoarsphenamine dose 0.6; two weeks apart, Wassermann became negative. Three more injections of neoarsphenamine were given, no mercury at any time.
317.	Wass. — H. W. —	Alc. — Chol. —	Alc. — Chol. —	Syphilis.	Thoroughly treated.
318.	Wass. — H. W. —	Alc. — Chol. —	Alc. — Chol. —	Lupus erythematosus.	
319.	Wass. — H. W. —	Alc. — Chol. —	Alc. — Chol. —	Syphilis.	Thoroughly treated.
320.	Wass. + + + + + H. W. + + + + +	Alc. — Chol. + + +	Alc. + + + + + Chol. + + + + +	Primary syphilis.	False negative to Lab. B.
321.	Wass. — H. W. —	Alc. — Chol. + + +	Alc. — Chol. +	Not syphilis.	Cholesterinized antigen gives false positive.
322.	Wass. + + + + + H. W. + + + + +	Alc. — Chol. —	Alc. + + + + + Chol. + + + + +	Parestis.	Strange in this case Lab. B is persistently negative on three different occasions.
323.	Wass. — H. W. —	Alc. — Chol. + + + + +	Alc. + + + Chol. + + + + +	Known case of syphilis.	Not treated for four years.
324.	Wass. — H. W. —	Alc. — Chol. —	Alc. — Chol. —	Varicose leg ulcer.	
325.	Wass. — H. W. —	Alc. — Chol. —	Alc. — Chol. —	Not syphilitic.	
326.	Wass. + + H. W. + + + + +	Alc. — Chol. + + + + +	Alc. + + + + + Chol. + + + + +	Tertiary syphilis.	False negative to Lab. B.
327.	Wass. — H. W. —	Alc. — Chol. —	Alc. — Chol. —	Not syphilitic.	
328.	Wass. — H. W. —	Alc. — Chol. —	Alc. + + + + + Chol. + + + + +	Known case of syphilis.	Insufficiently treated.
329.	Wass. + + + + + H. W. + + + + +	Alc. — Chol. + + + + +	Alc. + + + Chol. + + + + +	Tertiary syphilis.	Wassermann fast.
330.	Wass. — H. W. —	Alc. — Chol. —	Alc. — Chol. —	Active syphilis.	Unreliable blood report.
331.	Wass. + + + + + H. W. + + + + +	Alc. + + + + + Chol. + + + + +	Alc. + + + + + Chol. + + + + +	Primary and secondary syphilis.	
332.	Wass. — H. W. —	Alc. — Chol. —	Alc. — Chol. —	Treated syphilis.	Thoroughly treated.

TABLE I—CONT'D.

CASE NO.	LAB. A	LAB. B	LAB. C	CLINICAL DIAGNOSIS	REMARKS
333.	Wass. - H. W. -	Alc. - Chol. -	Alc. - Chol. -	Leucoplakia lower lip.	
334.	Wass. - H. W. -	Alc. - Chol. -	Alc. - Chol. -	Syphilis.	
335.	Wass. ++++ H. W. ++++	Alc. ++ Chol. ++++	Alc. ++++ Chol. ++++	Tertiary syphilis.	Patient has been under treatment for two years.
336.	Wass. - H. W. -	Alc. - Chol. -	Alc. - Chol. -	Not syphilis.	
337.	Wass. - H. W. -	Alc. - Chol. -	Alc. - Chol. -	Not syphilis.	
338.	Wass. - H. W. -	Alc. - Chol. ++	Alc. - Chol. +++	Syphilis.	Thoroughly treated.
339.	Wass. - H. W. -	Alc. - Chol. -	Alc. - Chol. -	Positive history of infection two years ago.	Insufficiently treated.
340.	Wass. - H. W. -	Alc. - Chol. -	Alc. - Chol. -	Syphilis.	Known case of syphilis. Thoroughly treated.
341.	Wass. - H. W. -	Alc. - Chol. -	Alc. +++ Chol. -	Syphilitic meningitis.	Positive history and positive clinical findings.
342.	Wass. - H. W. -	Alc. - Chol. -	Alc. - Chol. -	Not syphilitic.	
343.	Wass. - H. W. -	Alc. - Chol. -	Alc. - Chol. -	Positive history of syphilis.	No clinical symptoms present.
344.	Wass. ++++ H. W. ++++	Alc. ++++ Chol. ++++	Alc. ++++ Chol. ++++	Leucoplakia and tertiary syphilitic ulceration of tongue. Syphilitic glossitis with hypertrophy.	Neither diagnosed nor treated for 37 years. His brother is a well-known dentist.
345.	Wass. ++ H. W. ++++	Alc. ++++ Chol. ++++	Alc. ++ Chol. ++++	Positive history of syphilis six years ago.	This is a well-known physician who thought he was cured.
346.	Wass. - H. W. -	Alc. - Chol. -	Alc. - Chol. -	Treated syphilis.	Primary syphilis with positive Wassermann two months ago. Patient received six injections of 0.5 arsphenamine, one per week.
347.	Wass. ++++ H. W. ++++	Alc. ++++ Chol. ++++	Alc. ++++ Chol. ++++	Secondary syphilis.	Patient is a doctor's son. Case was never diagnosed.
348.	Wass. - H. W. -	Alc. - Chol. -	Alc. - Chol. -	Cerebrospinal syphilis.	Under treatment.
349.	Wass. - H. W. -	Alc. - Chol. -	Alc. - Chol. -	Not syphilis.	Husband examined 8-21-21. Wassermann was four-plus positive.
350.	Wass. - H. W. -	Alc. - Chol. -	Alc. - Chol. -	Syphilitic periostitis of right side of nose.	Known case of syphilis. Insufficient treatment.
351.	Wass. - H. W. -	Alc. - Chol. -	Alc. - Chol. -	Syphilis.	9-9-21. Primary syphilis; strongly positive Wassermann. He received 6 injections of salvarsan; one week intervals.



TABLE I—CONT'D.

CASE NO.	LAB. A	LAB. B	LAB. C	CLINICAL DIAGNOSIS	REMARKS
352.	Wass. — H. W. —	Ale. — Chol. + +	Ale. + + + + Chol. + + + +	Parasitis.	Twelve years ago infected with syphilis, treated for three years. Seven years later he was married. Infected his wife with an initial lesion of the cheek. Examination at this time showed active syphilis of the mouth with four-plus Wassermann. Took a little treatment and discontinued his visits. Two years later typical case of parasitis. Wassermann in this case is unreliable.
353.	Wass. — H. W. —	Ale. — Chol. —	Ale. — Chol. —	Lupus erythematosus.	
354.	Wass. — H. W. —	Ale. — Chol. —	Ale. — Chol. —	Not syphilitic.	
355.	Wass. — H. W. —	Ale. — Chol. —	Ale. — Chol. —	Reinfected case of syphilis.	Blood result unreliable.
356.	Wass. — H. W. —	Ale. — Chol. —	Ale. — Chol. —	Not syphilitic.	
357.	Wass. — H. W. —	Ale. — Chol. —	Ale. — Chol. —	Syphilophobia.	Patient never gave a history of syphilis, never showed any clinical symptoms. Wassermann test always negative, yet treated for syphilis. Thoroughly treated.
358.	Wass. — H. W. —	Ale. — Chol. —	Ale. hemolysed Chol. —	Syphilis 4 years ago.	Laboratory C, showed only slightly positive.
359.	Wass. + + + + H. W. + + + +	Ale. + + + + Chol. + + + +	Ale. + + + + Chol. + + + +	Primary syphilis.	This diagnosis was confirmed by a competent neurologist. Negative history.
360.	Wass. — H. W. —	Ale. — Chol. —	Ale. — Chol. —	Parasitis.	
361.	Wass. — H. W. —	Ale. — Chol. —	Ale. — Chol. —	Tuberculosis varicosis cutis tip nose.	
362.	Wass. — H. W. —	Ale. — Chol. —	Ale. — Chol. —	Ulcerated tubercular glands.	
363.	Wass. — H. W. —	Ale. — Chol. —	Ale. — Chol. —	Multiple cutaneous gumma.	
364.	Wass. — H. W. —	Ale. — Chol. —	Ale. — Chol. —	Syphilis.	Thoroughly treated.
365.	Wass. — H. W. —	Ale. — Chol. —	Ale. — Chol. —	Syphilis.	Ten years' duration. Thorough treatment.

\*Key to Wassermann reports: Wass.—Wassermann. H. W.—Hecht-Weinberg. Ale.—Alcoholic. strongly positive. + + + —Strongly positive, + —Borderline, — —negative, Chol.—Cholesterinized. + + + + —Very

From that date until Nov. 28, he received two injections of neosalvarsan and eight injections of mercury. On that day, both tests were still four-plus.

He was then given two injections of old salvarsan and five injections of mercury before Jan. 2, 1919. On that date, both tests were negative.

On the following day, he received an injection of old salvarsan. The next day, a provocative Wassermann was made and again both tests were negative. No treatment was given until July 8. On that day, both tests were one-plus. From then until Dec. 24, he received two injections of old salvarsan and five injections of mercury. Both tests were then negative.

From Jan. 8, 1920 to June 11, he received two injections of old salvarsan and six injections of mercury. On June 11, the report from Laboratory A was Wassermann one-plus, Hecht-Weinberg four-plus; Laboratory B, alcoholic and cholesterinized antigens negative. No treatment was given. On June 29, the report from Laboratory A, Wassermann and Hecht-Weinberg both four-plus; Laboratory B alcoholic and cholesterinized antigens both negative.

On Nov. 15, another test was reported from Laboratory A, Wassermann and Hecht-Weinberg negative; Laboratory B, alcoholic antigen negative and cholesterinized four-plus; Laboratory C, same as Laboratory B.

From that date to April 6, 1921, he received three injections of neoarsphenamine and one injection of mercury. Then another test was made, Laboratory A, reporting anticomplementary; Laboratory B, alcoholic antigen negative and cholesterinized antigen four-plus; Laboratory C, same as Laboratory B.

On April 11, the test was reported from Laboratory A, four-plus Wassermann and Hecht-Weinberg; Laboratory B, alcoholic antigen negative and cholesterinized antigen four-plus; Laboratory C, same as Laboratory B.

On April 16, a fourth laboratory reported a four-plus Wassermann and Hecht-Weinberg. From April 16 to July 11, he received one injection of arsphenamine and three injections of mercury. On the latter date the test was reported from Laboratory A, Wassermann and Hecht-Weinberg negative; Laboratory B, negative alcoholic antigen and four-plus cholesterinized antigen; Laboratory C, two-plus alcoholic antigen and four-plus cholesterinized antigen.

On the next day he received an injection of silver-salvarsan, dose 0.1. On the day following that a provocative Wassermann was reported from Laboratory A, Wassermann negative and Hecht-Weinberg two plus; Laboratory B, alcoholic antigen negative and cholesterinized antigen two-plus; Laboratory C, alcoholic antigen two-plus and cholesterinized antigen four-plus.

To complete the treatment patient received from July 26, 1921, to Sept. 3, 1921, weekly injections of silver salvarsan dose 0.2 and 0.3 gm. receiving in all seven injections. The reason this patient did not receive weekly injections of arsphenamine and mercury in the beginning was that he was in and out of the city, never remaining long enough to take a thorough course of treatment.

CASE 21.—W. S. Undetermined case of syphilis. No symptoms. Patient has an idea he has syphilis. Test made on July 30, 1920, was reported from Laboratory A, Wassermann negative and Hecht-Weinberg suspiciously positive; Laboratory B, alcoholic antigen negative and cholesterinized antigen four-plus.

From that day to November 3, he received two injections of old arsphenamine

and five injections of mercury. On that day, Laboratory A reported Wassermann and Hecht-Weinberg negative; Laboratory B, specimen lost; Laboratory C, both alcoholic and cholesterinized antigens four-plus.

No treatment was given from Nov. 31 to Feb. 1, 1921. Then the test was reported from Laboratory A, Wassermann and Hecht-Weinberg both four-plus; Laboratory B, alcoholic and cholesterinized antigens both negative; Laboratory C, alcoholic antigen two-plus and cholesterinized antigen four-plus. On Feb. 8 another test was made, Laboratory A reporting serum anticomplementary; Laboratory B, alcoholic antigen two-plus and cholesterinized antigen four-plus; Laboratory C, same as Laboratory B.

On Feb. 16, the test was reported from Laboratory A, Wassermann and Hecht-Weinberg negative; Laboratory B, alcoholic and cholesterinized antigens negative; Laboratory C, alcoholic antigen two-plus and cholesterinized four-plus.

Up to the present time November 26, I have been unable to determine whether or not this patient has or ever has had syphilis.

In conclusion, I wish to emphasize especially (1) the importance of thorough clinical examination to determine the presence of syphilis, (2) the need of the serologist to realize the responsibility they assume when issuing reports, either positive or negative; and (3) the need of a standardized dependable technic of the Wassermann test.

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## AN ARSPHENAMINE DERIVATIVE SUITABLE FOR SUBCUTANEOUS ADMINISTRATION\*

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(Received for publication, March 27, 1922)

IN 1910 Ehrlich introduced arsphenamine as a new and powerful remedy against syphilis. He advocated the intramuscular injection of this drug. The therapeutic results of the period of early trial were exceedingly gratifying; the lesions were freed from spirochetes in one to three days and healed in a few weeks. However, clinical experience very soon demonstrated that the intramuscular injection of the hydrochloride, the sodium salt or the suspension of the arsphenamine base in water gave rise to a severe local irritation involving considerable pain, and was often followed by extensive necrosis of the injected muscle. In order to avoid this local reaction Schreiber and Iversen introduced the intravenous administration of the sodium salt, and this mode of treatment has been generally adopted, although some clinicians have continued to advocate either intramuscular or subcutaneous injections, especially of neoarsphenamine and the intramuscular use of suspensions of either drug in oil.

Late in 1911, after almost two years of practical experience with arsphenamine, Ehrlich wrote as follows: "Die intramuskuläre Injektion hat eine nachhaltigere Wirkung als die intravenöse. Aber die Technik ist eine ausserordentlich schwierige und ruft manchmal unangenehme Folgeerscheinungen und Schmerzen hervor. In dieser Beziehung ist die intravenöse Injektion, zumal wenn der 'Wasserfehler' eliminiert wird, für Arzt und Patienten viel bequemer. Sie ist allerdings wegen der schnellen Ausscheidung weniger wirksam und muss daher im Prinzip stets wiederholt werden. Ich glaube daher dass die intravenöse Injektion wohl allgemein angewandt werden wird und dass man die intramuskuläre oder subkutane Injektion der verschiedenen Emulsionen und Suspensionen besonders für Fälle

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\*(Approved for publication by the Surgeon General.) Division of Pharmacology, Hygienic Laboratory, U. S. Public Health Service.

aufsparen wird, in denen durch bestimmte Kontraindikationen (Herzfehler, Nervenaffektion) ein besonders vorsichtiges Handeln geboten ist."

This statement of the discoverer of arspenamine is significant, for it shows that the intravenous method was adopted in order to eliminate the local reactions and for no other reason. Moreover, intramuscular injections were believed to be more effective therapeutically and less dangerous. Subsequent experience, now extending over 10 years has not altered the situation essentially. The careful work by Colonel Craig of the U. S. Army and of Colonel Harrison of the British Army has clearly shown that intramuscular injections are more effective upon the Wassermann reaction and the lesions.

While the intravenous method of administration yields very satisfactory results in the hands of experienced clinicians, this mode of treatment involves some technical difficulties, among which may be mentioned the difficulty of intravenous medication in excessively adipose patients and in young children, where the veins are often not accessible. In infants, injection of the drug into the longitudinal sinus has been resorted to, but as such experienced a clinician as Fordyce has recently pointed out with regard to this method, "the technical difficulties have been so great that in the hands of the inexperienced more harm than benefit has often resulted."

Continued efforts have therefore been made by Wechselmann, Fordyce, Harrison and many others to develop a subcutaneous or intramuscular method suitable for such cases, even by the general practitioner. It is not the aim of this paper to review the various methods which were devised for this purpose, suffice it to say that neoarsphenamine was usually advocated, in preference to arspenamine, given intramuscularly or subcutaneously as a rule in very concentrated solution (0.1 to 0.2 gm. in 3 c.c. of water), with or without the addition of local anesthetics. Fordyce and Rosen (1920) mention slight infiltration in two among 45 infants treated with intramuscular injections of neoarsphenamine. Harrison, White and Mills (1917) state that some of their patients treated subcutaneously or intramuscularly with neoarsphenamine often complained of pain at the site of injection lasting for a week or longer, making the patient lame and preventing his sleeping on the same side. At its

worst it was not nearly so severe as an intramuscular injection of arsphenamine, but might be compared with a bad mercurial or calomel injection. Local swelling resulted. Wechselmann reports his experience with several thousand subcutaneous injections of neoarsphenamine and describes his technic in minute detail. He lays stress upon injecting the drug solution not intradermally, nor into the subcutaneous fat, but so that it is just deposited upon the fascia. In this case absorption is rapid and the pain if present lasts only a short time. It must be admitted that his technic requires considerable experience.

Apart from the local reaction which may or may not follow the subcutaneous or intramuscular injection of neoarsphenamine it has been pointed out by Harrison and others that the danger of acute toxic reactions is much less than after intravenous injections. It is true that in order to firmly establish this point it would require well controlled large series of selected cases, treated by both methods with the same drug, the same dose, and the same interval between doses.

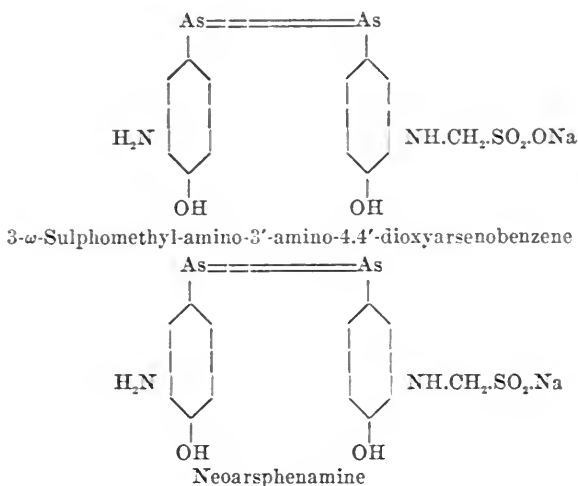
What has been said very briefly summarizes the advantages and disadvantages of the various methods of administration of arsphenamine and its derivatives. It would therefore appear that further search for an arsphenamine derivative which might be injected with impunity either subcutaneously or intramuscularly is called for, provided that such a drug is equal in therapeutic potency to arsphenamine or its well-known substitutes.

The purpose of this paper is to report some experimental work dealing with an arsenical closely related to neoarsphenamine which appears to possess the necessary requisites from the standpoint of the pharmacologist and to stimulate clinicians to give this drug a trial, so as to test the accuracy of the few published clinical reports dealing with this compound.

#### CHEMICAL PROPERTIES

The drug is obtained by treating arsphenamine base in aqueous suspension with formaldehyd and sodium bisulphite. To the resulting solution hydrochloric acid is added until complete precipitation has occurred. The precipitate after filtration is then converted into the sodium salt.

The compound is supposed to have the following constitution:



Its similarity to neoarsphenamine is seen from the above formula. Its preparation is covered by a German patent (D. R. P. 249726), and it has been manufactured in France since 1919 by the Laboratoire de Biochemie médicale, R. Pluchon in Paris.\* According to this French firm it is supposed to be very stable in aqueous solution, a distinct advantage over neoarsphenamine. In our work we have tested two different lots of French manufacture with an arsenic content of 17.76 and 17.24 per cent respectively.

The drug as received in sealed glass ampoules is a yellow powder. On opening the ampoules a slight sulphurdioxide odor is noticed. The powder dissolves very easily in cold water, leaving no insoluble residue. The solution is slightly acid to litmus, pure yellow in color, and does not show any color change or precipitate formation when exposed to air for 24 hours at room temperature. The drug is sold as the sodium salt and it is therefore not necessary to add alkali to prepare the solution for injection.

#### TOXICITY

The toxicity was determined in albino rats according to the official intravenous method, and also by subcutaneous injection into rats. In either case the animals were kept under observation for at least a week; the surviving animals were killed with chloroform and a necropsy made.

\*The French trade name for the preparation is Sulfarsenol.

TABLE I  
TOXICITY

DRUG LOT NUMBER	DOSE		INTRAVENOUS INJECTION			SUBCUTANEOUS INJECTION		
	MILLIGRAMS PER KILLO	C.O. I/100 ARSEN- IC EQUIVALENT PER KILLO	NO. OF RAT	RESULT + = DIED - = SURVIVED	TIME OF DEATH OR DISCHARGE	NO. OF RAT	RESULT + = DIED - = SURVIVED	TIME OF DEATH OR DISCHARGE
No. 1	300	71	1	+	48 hours	16	+	48 hours
			2	+	4 days	17	+	4 days
			3	+	4 days	18	+	5 days
			4	+	4 days	19	+	6 days
			5	+	5 days	20	+	6 days
	260	61.3	6	+	4 days	21	+	4 days
			7	-	8 days	22	+	4 days
			8	-	8 days	23	-	8 days
			9	-	8 days	24	-	8 days
			10	-	8 days	25	-	8 days
No. 2	220	52.1	11	-	26 days	26	+	5 days
			12	-	26 days	27	-	26 days
			13	-	26 days	28	-	26 days
			14	-	26 days	29	-	26 days
			15	-	26 days	30	-	26 days
	400	91.9	31	+	72 hours	46	-	15 days
			32	+	72 hours	47	-	15 days
			33	+	4 days	48	-	15 days
			34	-	15 days	49	-	15 days
			35	-	15 days	50	-	15 days
	340	78.1	36	-	10 days	51	-	10 days
			37	-	10 days	52	-	10 days
			38	-	10 days	53	-	10 days
			39	-	10 days	54	-	10 days
			40	-	10 days	55	-	10 days
	300	68.9	41	-	10 days	56	-	19 days
			42	-	10 days	57	-	19 days
			43	-	10 days	58	-	19 days
			44	-	10 days	59	-	19 days
			45	-	10 days	60	-	19 days



The data relating to toxicity are compiled in Table I, the dose being expressed as milligrams or as number of cubic centimeters of a 1/100 arsenic equivalent solution per kilo body weight. It will be seen that the toxicity of the two lots of drug differs somewhat, a common experience met with all arsenobenzene derivatives. The minimum lethal dose of Lots No. 1 and No. 2 is 300 and 400 mg., respectively, when the drug is given by vein, and 300 and greater than 400 mg., respectively, after subcutaneous injection. Hence the toxicity of the drug compares very favorably indeed with that of the average commercial lots of neoarsphenamine.

No acute toxic reactions were ever observed in these animals, a point which also seems to speak in favor of this preparation.

Late toxic symptoms occurred in the majority of the animals which had received fatal doses or doses closely approaching the fatal threshold. In these cases the animals exhibited tremors beginning with the second or third day after the injection, and persisting until death. This symptom is also observed in rats treated with comparable doses of neoarsphenamine. The animals which received up to  $\frac{3}{4}$  of the fatal dose remained perfectly normal, and often showed a considerable gain in weight, 10 to 20 per cent in 10 days to 2 weeks.

The gross pathologic findings of animals injected with lethal doses were mostly confined to the kidney, which appeared at times enlarged, edematous and pale and in some animals had the typical appearances of a "white arsenic kidney." The so-called red arsenic kidney was never seen. The liver rarely showed any obvious change, this if occurring being confined to a hazy appearance of the lobules and congestion. A few animals had partly congested lungs, and the pleural cavity contained a clear transudate. To sum up, the gross lesions are very similar to those produced by neoarsphenamine, and involve principally the kidney.

*Trypanocidal Action.*—We have for the last two years tested out a quantitative method which permits us to appraise the parasitocidal value of arsenicals on rats infected with *Trypanosoma equiperdum* accurately and requiring only two to three days for each test. The details of this method, which has yielded important results concerning the nature of the chemotherapeutic action of arsenicals, have been published in various papers in the *Journal of Phar-*

*macology and Experimental Therapeutics.* Extensive application of the method to a great variety of arsenicals which had been tested by others on spirochete infections has shown that the results obtained by means of our trypanocidal test agree very well indeed with the spirocheticidal test in rabbits. The method has of course its limitation, inasmuch as it does not furnish absolute evidence of the spirocheticidal value of a new arsenical, if this drug has not been shown previously to be effective in spirochete infections. This having been established however, then our method is very useful for appraising in a quantitative way the relative parasiticidal action of the new drug as compared with that of other arsenicals. It is far superior from the quantitative standpoint to any other method, as it measures the killing power of a given dose of drug for a certain definite number of parasites, the latter being estimated in the blood with the same accuracy as red or white blood cells.\*

Table II includes the data on the trypanocidal activity of the two lots of the drug. In the column headed "Initial count," the number of trypanosomes per cubic millimeter of blood is given, as found just before injection of the drug. The following column contains the result of the blood examination 24 hours afterwards, a negative sign indicating absence of trypanosomes in a large number of fields of a blood drop. The table needs no further comment, than to state that the drug exhibits a very powerful parasiticidal effect, which is slightly greater after subcutaneous than after intravenous injection. It may here be pointed out that Voegtlin and Smith have found some time ago with the same methods as regards trypanocidal effect a superiority of the intramuscular over the intravenous mode of administration of arsphenamine. The parasiticidal action of the new drug is slightly less than that of the average commercial neoarsphenamine.

The speed of the trypanocidal action also compares favorably with that of neoarsphenamine, the principal effect of minimum effective doses being brought about within 24 hours.

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\*It should not be forgotten that any toxicity or therapeutic efficiency test of a drug is obviously restricted in value on account of the fact that the human species cannot be used and that different species have shown quantitative if not qualitative differences in behavior towards drugs. In the case of the official toxicity test for arsphenamine and its substitutes a large experience has shown that differences of toxicity of different products as determined in rats, show also similar differences when tested clinically, hence the usefulness of the rat test.

TABLE II  
TRYVANOCIDAL ACTION

DRUG LOT NUMBER	DOSE C.C. 1/100 ARSENIC EQUIVALENT SOLUTION PER Kilo	INTRAVENOUS INJECTION			SUBCUTANEOUS INJECTION		
		INITIAL COUNT	24 HR. EXAM.	48 & 72 HR. EXAM.	INITIAL COUNT	24 HR. EXAM.	48 & 72 HR. EXAM.
No. 1	10.0	184,000	trace	-			
	"	118,000	-	-			
	"	124,000	-	-			
	7.5	115,000	-	-	100,000	-	-
	"	128,000	-	-	100,000	-	-
	"	176,000	8,000	+	102,000	-	-
	5.0	140,000	-	-	202,000	-	-
	"	120,000	72,000	++	240,000	-	-
	"	146,000	30,000	+++	144,000	6,000	++
	3.5	160,000	80,000	+++	152,000	16,000	+++
No. 2	"	160,000	200,000	++++	110,000	3,000	trace
	"	128,000	152,000	++++	92,000	30,000	++++
	10.0	140,000	-	-			
	"	150,000	3,000	-			
	"	146,000	-	-			
	7.5	200,000	6,000	trace	104,000	-	-
	"	192,000	trace	-	140,000	-	-
	"	170,000	6,000	-	102,000	-	-
	5.0	150,000	69,000	+	130,000	24,000	+++
	"	124,000	6,000	-	152,000	54,000	++++
	"	112,000	128,000	++++	200,000	6,000	+
	3.5	118,000	240,000	++++	116,000	60,000	++++
	"	100,000	14,000	trace	200,000	120,000	++++
	"	100,000	8,000	-	104,000	36,000	++++

## RATE OF EXCRETION

It has been pointed out by us in a recent paper (Voegtlin and Thompson, 1922) that the rate of excretion of the arsenic of all classes of arsenicals is an important factor governing both toxicity and parasitocidal action. It was shown that variations in rate of elimination of the drug from the body may account, partly at least, for some of the toxic reactions observed in some patients. Prolonged retention favors the toxic as well as the parasitocidal effect. The data furthermore indicated that arsphenamine and its substitutes exhibit the optimum rate of elimination, and this is one reason why this drug is of practical value. It was therefore of interest to study the rate of excretion of the arsenic of the new compound and to compare it with that of arsphenamine and the other well-known arsenicals. The technic used was the same as in the work just mentioned. Albino rats received intravenous or subcutaneous injections. The urine and feces were collected quantitatively at certain periods and were analyzed separately for arsenic. The data are compiled in Table III. Attention is called to the fact that the rate of excretion after subcutaneous administration is almost the same as after intravenous injection. This is undoubtedly due to the fact that the subcutaneous injection does not cause any appreciable local irritation which might reduce absorption.

The magnitude of the urinary excretion of the drug falls within the same range as that of arsphenamine, neoarsphenamine and silver arsphenamine. Variations in rate are also in evidence between different rats. In this respect this compound behaves similarly to arsphenamine and neoarsphenamine.

## STABILITY OF AQUEOUS SOLUTIONS

In order to test the accuracy of the claims made by the manufacturer, viz., that this drug is very stable in solution, the toxicity of an 8 per cent solution which had stood at room temperature (25° C.) exposed to air for 24 hours was determined. It was found that the toxicity of this solution had not increased. Dr. Johnson of this laboratory tested the aqueous solutions by a method which indicates oxygen-absorption. During six hours the drug solution kept at 37° C. did not absorb any oxygen from air, whereas neoarsphenamine under the same conditions showed marked oxidation.

TABLE III  
RATE OF SECRETION OF ARSENIC

NO. OF RAT	INTRAVENOUS INJECTION				SUBCUTANEOUS INJECTION				
	URINE		FECES	TOTAL EXCRETION	URINE		FECES	TOTAL EXCRETION	
	6 HOURS	24 HOURS			6 HOURS	24 HOURS			
247	22	31	35	66	20	39	16	55	
248	18	31	30	70	16	34	36	70	
249	22	32	20	52	19	40	21	61	
250	27	29	19	48	7	23	43	66	
251	23	38	16	54	29	47	24	71	
Average	22	32	26	58	18	37	28	65	

The chemical test therefore agrees with the toxicity test. This stability of aqueous solutions is probably due to the acidity of the solution (acid to litmus). From the sulphur content it would furthermore appear that the drug contains some uncombined sulphite, which of course would stabilize the preparation.

#### LOCAL REACTION AND TECHNIC FOR SUBCUTANEOUS INJECTION

Numerous animal experiments were carried out in order to study the local effect of subcutaneous injections of the drug and to furnish information regarding the best technic to be used for avoiding local irritation. These experiments were made on albino rats and rabbits. Neoarsphenamine given in the same concentration was used for comparison. Only one protocol is herewith given as an illustration.

Rabbit—2.25 Kg. This animal received four injections of the new drug on the same day in four different places in the back, as follows:

- A. 0.1 c.c. of a 120 per cent solution subcutaneously.
- B. 0.6 c.c. of a 20 per cent solution subcutaneously.
- C. 0.1 c.c. of a 120 per cent solution intradermally.
- D. 0.6 c.c. of a 20 per cent solution intradermally.

Examination of the rabbit for local reaction 48 hours later:

- A. Slight thickening of skin, otherwise normal.
- B. Practically normal.
- C. Black necrotic area, 0.75 cm. in diameter, surrounded by a narrow, reddened area with considerable thickening of subcutaneous tissue.
- D. Slight thickening of skin.  
No change on third day.

Fourth day:

- A. and B. Normal.
- C. No change.
- D. Small scab has formed.

Sixth day:

- A. and B. Normal.
- C. Black necrotic area 0.75 cm. in diameter, surrounded by halo of yellowish white appearance with sharply defined outline and this again surrounded by slightly reddened area showing marked thickening.

- D. White yellow area 0.6 cm. in diameter sharply defined, surrounded by very slight reddening, very little thickening of skin and subcutaneous tissue.

Tenth day:

No change in local reactions.

Fourteenth day:

A. and B. Normal.

C. Black necrotic area 0.75 cm. in diameter surrounded by yellowish zone 0.5 cm. diameter, marked thickening, but no erythema.

D. Yellowish slightly hardened area,  $0.5 \times 0.75$  cm. in diameter. Scab forming.

Thirty-ninth day:

A. and B. Normal.

C. Hard, solid scab  $1.75 \times 1.25$  cm. in diameter.

D. Scar healed, hair growing over it.

Seventy-sixth day:

All lesions healed.

Together the four doses given to this rabbit fall slightly below the fatal dose for this species and therefore, each separate dose was approximately one-fourth of the maximum tolerated dose. The protocol of this experiment clearly shows that even such large doses are well tolerated, provided care is taken to avoid injection *into* the skin (intradermal). When this occurs local necrosis invariably follows and the injury requires several weeks for repair. It is, however, very simple to avoid this trouble by a little care. With regard to the optimum concentration of the drug we would advocate on the basis of our experience with animals that a 20 per cent solution in sterile water be used for subcutaneous injection. With this concentration we have never observed any local irritation to follow. The control experiments with neoarsphenamine have shown that the local irritation is always noticeable and often very intense.

#### CLINICAL REPORTS

The efficacy of the drug in the treatment of syphilis has so far been tested only on a relatively small number of cases, by Lévy-Bing, Lehnhoff-Wyld and Gerbay (1919), Yernaux and Bernard (1919), Carminow Doble (1920) and Crawford and Fleming (1921). The size of the therapeutic dose has not been determined. On the

basis of the trypanocidal power it would appear that doses slightly greater than those customary for neoarsphenamine might be used.

#### CONCLUSION

A derivative of arsphenamine, prepared from arsphenamine, formaldehyd and sodium sulphite, has been studied experimentally.

The following conclusions have been reached:

1. The drug appears to be well suited for clinical use on account of its great solubility in water, the stability of its solutions in the presence of air, and the absence of any local irritation following its subcutaneous injection.

2. The toxicity of the drug is about the same as that of an average commercial preparation of neoarsphenamine.

3. The trypanocidal power of the two lots tested is slightly less, weight per weight, than that of the average neoarsphenamine.

4. The rate of excretion of the arsenic of the drug is of the same order as that of arsphenamine and neoarsphenamine.

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## AN UNUSUAL REACTION FOLLOWING ANTILUETIC TREATMENT, WITH A DISCUSSION OF THE JARISCH-HERXHEIMER REACTION

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(Received for publication December 8, 1921)

IT appears at the present time that considerable misunderstanding exists as to what is meant by the Jarisch-Herxheimer reaction, or as it is more commonly known, the Herxheimer reaction. This fact was brought to our attention in talks with colleagues and on reviewing the literature on the subject.

In a case in our care undergoing antiluetic treatment, an extraordinary reaction occurred. Believing it to be a Herxheimer, and in order to determine whether or not it would be advisable to continue salvarsan medication, a search of the literature was made to see what had been done in similar cases. We found no symptoms identical to ours, but we did find that the term "Herxheimer reaction" was often used incorrectly.

The following case which presents several unusual features, is presented in detail:

J. M., white, male, aged thirty-three years. He had had measles and mumps in childhood, no operations and no accidents. He gave a history of gonorrhea twice with no complications. A sore appeared on the penis 12 years ago, 10 days after intercourse, and disappeared in 4 days without any treatment. There were no symptoms of secondary lesions following this sore. In 1918 when in the Navy he had a Wassermann test which he believes was negative, as he received no antiluetic treatment.

The patient brought his wife for examination. She complained of sores in the mouth. On examination they proved to be papular syphilids. The husband denied having had any other sore on his body at any time with the exception of the sore on his penis 12 years previously. The blood Wassermanns of both the patient and his wife were three-plus.

The skin was clear, there was no rash and no indication of secondary lesions of the skin or mucous membranes. The hair was thick and no alopecia. The lungs were negative and the heart normal in size with no murmurs heard. The abdomen was negative, the liver and spleen not palpable. The pupils were equal and reacted actively to light and accommodation. The patellar reflexes were present,

not exaggerated. The inguinal and epitrochlear glands were palpable, the posterior cervicals not demonstrable. The blood pressure was 118 systolic, 84 diastolic.

The urine was neutral in reaction, no albumin or sugar, sp. gr. 1016. On April 16 the patient received 0.45 gm. French neoarsenobenzol (Sanar) intravenously. The powder was given in concentrated form. His wife received the same dose. Five days later 0.9 gm. of the same product in concentrated solution was injected. The wife received 0.6 gm. Three days later the patient received 0.008 gm. mercury and 0.016 gm. metallic arsenic intravenously. The wife received the same medication.

The next day the patient complained of itching of the right lower leg. Examination showed a reddened urticarial wheal the size of a man's hand over the inner portion of the right tibia. The itching was confined to this spot. Nothing was thought of the lesion and the patient was given 0.9 gm. neoarsenobenzol. His wife was given 0.6 gm.

The next morning I was called in. The patient complained of intense itching over the entire body. His temperature was 101.2° F. His hands were so greatly puffed up that the tense skin caused pain and the patient was unable to close his fists. The feet were so swollen that shoes could not be worn. There was marked edema of both legs, with pitting on pressure. Over the entire body there were huge urticarial wheals which were most pronounced wherever there was pressure on the skin, as on the back, the buttocks and about the waist. The wheals were raised, felt hot and were dusky red in color. The patient was sent to the hospital the same day.

Several complete urinalyses were done while he was there. In no specimen was there any albumin, nor were there any red blood cells. An occasional granular cast was seen.

A phenolsulphonephthalein test done on the third day after admission showed a two hour elimination of 65 per cent.

The patient never had any gastrointestinal disturbances, no falling out of the hair, or brittleness of the nails. None of the symptoms of arsenic poisoning were present.

Unfortunately, the blood pressure was not taken at this time. We did not believe that any change would be found, as the urinary tract was not involved. However, cases of lowering of blood pressure have been reported.

The patient remained in the hospital six days. He received hot bakes, catharsis and adrenalin chloride subcutaneously. The generalized edema became less and less as did also the itching and skin reaction. There was no desquamation of the skin at any time. On discharge the patient felt perfectly well and all signs of his acute condition had disappeared.

He remained under observation and without any treatment for five weeks. At the end of this time he was put on mercury rubs, receiving four rubs a week. This was continued for two weeks. He was then given mercury cyanide intravenously every third day for six treatments. The patient felt perfectly well, had no untoward symptoms, so 10 days later he was given 0.1 gm. French neoarseno-

benzol (Sanar). In order to avoid the possibility of an anaphylactic shock the procedure advocated by Stokes<sup>1</sup> was followed.

Four days later the patient was given 0.6 gm. of the same medicine. He was then given a course of five full injections of neoarsenobenzol, preceded each time by an injection of atropin as suggested by Stokes.

No mercury was given until we had finished the arsenic injections.

At the present time the man is still under mercurial treatment. He has felt perfectly well and has had no ill effects since his previous severe reaction.

A point of interest is the fact that his wife was receiving the same treatment, using the same distilled water, the same technic and still she had no reaction following the injections.

One may question the right to use concentrated solutions of neoarsenobenzol. However, while on duty in the Venereal Hospital of the Intermediate Section S.O.S. in France, this same drug was given in the same concentration in hundreds of cases. We do not remember having seen one case in which an unusual reaction occurred following its injection.

At first we believed that we were dealing with a case showing the Herxheimer reaction. However, on reading the original articles it soon became evident that this case did not belong to that category, but was more on the order of an anaphylactoid reaction.

In 1895 Jarisch<sup>2</sup> presented a long series of cases affected with syphilitic roseola in whom a reaction occurred which manifested itself in an increase in the local appearances of the disease. This phenomenon occurred during the first days of the administration of mercury in insoluble form. Jarisch observed that after the administration of 2 to 5 inunctions or injections the individual spots became much more distinct than before. No further mention was made of this observation until seven years later Herxheimer and Krause<sup>3</sup> reported remarkable changes in the skin rash of syphilis after the administration of insoluble mercury salts. They stated that the characteristic reaction appeared only when a sufficient quantity of mercury was absorbed suddenly and for the first time. The reaction appeared only after the first large dose, never with any later doses. The exanthem changed in appearance in from fifteen to twenty-four hours after injection. The efflorescences became greater. Roseolar spots, formerly not noted, came to light. The efflorescences always showed a marked prominence in the skin, so that they looked more like urticarial than erythematous papules.

The rash sometimes became confluent and changed in color from a dusky red to bright red.

The authors stated that this reaction showed only in the general exanthem of early syphilis. By experiments, they showed that the phenomenon was not due to mercurial poisoning. Corroboration of this observation came from all sides and the reaction since then has been termed the Jarisch-Herxheimer reaction. As will be noted, this was described before the advent of arsenic in the treatment of syphilis.

With the discovery of salvarsan by Ehrlich and its constantly increasing use, the Herxheimer took on a new and greater significance.

Finger<sup>4</sup> reported several cases of secondary skin lesions which reacted in the same way after salvarsan treatment that Jarisch and Herxheimer had described after mercury medication.

Beck<sup>5</sup> described a skin reaction accompanied by a unilateral paralysis of the vestibular nerve. He called this a Herxheimer reaction in the region of the 8th nerve.

When salvarsan was first used and given subcutaneously instead of intravenously, an edematous reddened area of reaction appeared about the infiltrate. This was often incorrectly spoken of as the Herxheimer reaction.

Friedlander<sup>6</sup> made no differentiation between anaphylactic reaction and the Herxheimer reaction.

Many assumptions have been brought forth as to the etiology of this reaction. Jarisch<sup>2</sup> believed that the mercury had not only a direct antiparasitic action, but also a healing influence on the products of syphilis. Herxheimer<sup>3</sup> and Krause believed it to be due to a hypersensitiveness to mercury of the cells which are affected with syphilis. Wechselman<sup>7</sup> believed that the reaction was due to the formation of toxic bodies through the action of the spirochetes and the antigens.

Guy<sup>8</sup> stated that the reaction was due to the stimulating activity of small, nonsterilizing doses of arsphenamine, and that it could be avoided by giving full therapeutic doses. This last idea is in accord with the fact that in former years when small doses were given the Herxheimer reaction was not so uncommon, whereas, today when we use large, repeated doses it is seldom observed.

## CONCLUSIONS

Many reactions occurring at all stages of syphilitic infection have been incorrectly called Herxheimer reactions. By the Jarisch-Herxheimer reaction is meant a sudden intensification of the secondary syphilitic lesions of the skin or mucous membranes after a first dose of insoluble mercury or of salvarsan.

At the present time, when, with the aid of the dark-field and Wassermann test, the treatment of syphilis with large repeated doses of salvarsan is begun before the onset of the secondary stage, the Herxheimer reaction is most uncommon and is really more of historical than of practical interest.

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## DEATH FIFTY-FIVE HOURS AFTER THE INTRAVENOUS ADMINISTRATION OF NEOSALVARSAN

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(Received for publication, March 10, 1922)

**B**ECAUSE of the universal use of neosalvarsan in the treatment of syphilis, the following case report of a death, presumably due to its use, will be of interest, especially as the postmortem examination showed no other cause of death.

R. S., white male, aged thirty-five years, a syphilitic of fifteen years' duration, was given 0.6 gm. of neosalvarsan intravenously on Dec. 3, 1921, at 2 p. m. The following day his companions in a pool room noticed that he acted "dopey." The next day they stated that he sat motionless in a chair all afternoon. At 5 p. m. (51 hours after the injection) he had a convulsion and pitched forward out of his chair striking the floor with his face. This caused a laceration of the bridge of the nose and he was said to have lost between a pint and a quart of blood. He became unconscious immediately, but soon had another convulsion and became comatose. The convulsions continued until death ensued four hours later.

Two courses of treatment had been given in the six months preceding death. The first course consisted of eight salvarsans of 0.4 to 0.6 gm. each and the second of six silver-salvarsans of 1.5 to 0.3 gm. each. No reaction had been noted in either series of treatments. Inunctions of mercury and the internal administration of potassium iodid was continuous during the treatment, except during the course of the silver-salvarsan injections. The last dose of the latter was administered six weeks previous to the dose of neosalvarsan given before death. All salvarsans, with the single exception of neo, were given by myself.

The postmortem examination, conducted by Dr. T. P. McNamara, pathologist of Finley Hospital, was held 24 hours after death and after the body had been embalmed. No gross lesions which might have caused death were demonstrated. Evidences of embolism or

thrombosis were sought for in the brain with the greatest care, but could not be found. The only lesions of recent origin that were encountered were hemorrhages into the ethmoidal cells, maxillary and sphenoidal sinuses though no fracture of the adjacent bones could be demonstrated.

The microscopic studies showed an acute congestion of the kidneys, hyaline necrosis of some of the glomerular tufts and a patchy necrosis of the cells of the convoluted tubules. The collecting tubules showed a tendency of the epithelium to slough but this might well have been a postmortem change. The liver showed very slight central necrosis and a periportal fibrosis and plasma cell infiltration, i. e., the lesion described by Warthin as characteristic of syphilis. In many of the sections the endothelium of the arteries was swollen and in some instances appeared hyalinized. Mr. H. A. Grimm, chemist at the Finley Hospital, tested the kidneys and liver for arsenic by Marsh's method but could not demonstrate it in several attempts. Unfortunately the urine had been rejected and was not tested.

The fact that this man, with no anatomical lesion which would explain his death, fell ill soon after the administration of neosalvarsan is strong presumptive evidence that the arsenic compound was the cause of death. Furthermore, this supposition is supported by the convulsions and coma preceding death and by the microscopic changes in the kidneys and blood vessels, which appear to be of a toxic nature. No explanation can be given as to why arsenic was not found in the liver and kidneys, as it is usually stated that salvarsan arsenic is retained in the body tissues for from two to eight weeks. Various reports of coma and convulsions preceding death are found in the literature. These symptoms may appear from two to fourteen days after the administration of the drug.

# A CONTRIBUTION TO THE ACTION OF ARSPHENAMINE AND MERCURY ON THE TREPONEMA PALLIDUM

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(Received for publication, April 22, 1922)

SINCE Ehrlich's famous discovery of salvarsan and neosalvarsan there have been various opinions as to the action of these drugs on *Spirocheta pallida*.

It was thought at first that they were direct and powerful spirocheticides.

Hata, in 1910, pointed out that salvarsan does not kill the spirochetes of relapsing fever in the test tube even in very high concentration. Plaut and others, 1910-1911, stated that *Spirochaeta pallida* are not killed by high concentration in the test tube. Levaditi taught, and this theory has been generally accepted, that salvarsan becomes active only after passing through the liver. Noguchi found that defibrinated blood increased the spirocheticidal activity of salvarsan.

Though arspenamine fails to kill the spirochetes in the test tube yet when introduced into the body, either by intravenous or intramuscular injection, it becomes a powerful spirocheticide. Of this there is an abundance of clinical proof in our treatment of syphilis. This discrepancy between its action in vitro and in vivo still remains a mystery and the object of this paper is to state briefly a few experiments conducted along this line and to summarize the conclusions reached.

First, an alkaline solution of arspenamine 1:130 was prepared. A suspension of treponema was secured from a well developed chancre or, preferably a case of secondary syphilis with large, moist mucous patches, in which from 10 to 30 treponemata were to be found in each microscopic field. A suspension was made by placing a drop from a capillary pipette from each, on a cover glass and thoroughly mixed with a capillary pipette then covered with a slide; sealing the edges of the cover glass with vaseline to prevent drying and was examined with the dark-field apparatus at fifteen



minute intervals for two hours, then at hourly intervals for 8 hours longer. Some of the parasites were found to be alive and actively motile at the end of this observation.

Second, neoarsphenamine in the same dilution, in sterile water, gave the same results with similar suspension of spirochete.

Third, silver-salvarsan in dilution of 1:125 showed no increased spirocheticidal action over the two former solutions.

These experiments were found to correspond to those of above mentioned writers.

Struhmer in experimenting with trypanosomes found that the curative action of unheated salvarsanized serum lasted 24 hours and that its protective action lasted 48 hours while with the heated serum the curative action was still present at the end of three days. In comparing the relative values of salvarsan and neosalvarsan he found that whereas the former was still active after 48 hours and often 72 hours, neosalvarsan lost its parasitocidal powers after 24 hours.

While this may be true of trypanosomes in general, yet it remains to be proved that treponemata belong to this group and experiments done by me do not confirm the above results, as the following will illustrate: Salvarsanized and neosalvarsanized serum was obtained from blood drawn at two hour intervals for 12 hours, also 24, 36 and 48 hours respectively following intravenous injections, the blood being allowed to clot and the serum collected and divided into equal quantities. One was inactivated at 56° C. for one-half hour and the other preserved until used. A capillary drop of each was secured and mixed with a fresh suspension of treponemata and observed with dark-field apparatus at 15 minute intervals for two hours, then hourly for 12 hours. The same technic of mixing was used here as with the salvarsan solution. Motility was demonstrated in some of the parasites of each specimen of both active and inactivated salvarsanized and neosalvarsanized serum at the end of these observations, proving that the parasitocidal power of salvarsanized serum is no greater than the solution before intravenous injection and therefore Levaditi's contention of liver activation was not substantiated.

When a case of primary or secondary syphilis with open lesions, in which a dark-field shows numerous parasites, receives a full dose of either arsphenamine or neoarsphenamine and dark-field examina-

tions are made at four to eight hour intervals for 72 hours a different picture is seen. An appreciable diminution in the number of parasites is noted, beginning in about 12 hours and in 24 hours only a few can be found while in 48 to 72 hours repeated dark-field examinations usually fail to show any parasites whatever in the lesions.

To explain this some writers have suggested that arsphenamine increases the patient's immunity by stimulating the leucocytes and endothelial cells to greater activity. Volgthin and Smith hold that it is a direct spirocheticide, that the arsenobenzol group is oxidized to the trivalent oxide type before it kills the spirochetes and that the trivalent oxides of the general type RAsO are the only forms of arsenic which exert any direct action either on the protozoal or upon the host.

Myers recently stated (personal communication) that the leucocytes take up the arsphenamine in the blood stream and deposit it in the tissues. Noguchi has shown that in cultivating treponemata a piece of fresh animal tissue of the same animal to which treponema had become adapted was necessary to secure its growth artificially. From this we learn that the treponema derives its nourishment almost exclusively from the cellular protein. Assuming this to be true we have evidence for believing that we have found the way in which arsphenamine exerts its influence on the parasite as the drug in a fine crystalloid state in circulating through the capillary system passes through the thin endothelial membrane of the capillaries by a process of diffusion and osmosis, the arsenobenzol group, the group of greatest affinity, attaches itself to the cellular protein producing an arseno-protein which is not only unfavorable as a culture medium but is poisonous to the parasite. This is especially true of the cellular protein in and around the base of a syphilitic lesion. Here the cells are already damaged by the spirotoxin and more permeable to the arsenic radical. We have clinical evidence of this in that an area of redness is often seen around a syphilitic lesion 24 to 48 hours following arsphenamine injection and that the patient will often complain of increased heat, pain and tenderness in this area. Further proof of this is furnished by excising a small piece of this tissue in the stage of reaction, grinding it to a fine paste with normal salt solution and mixing with a fresh suspension of treponema. In marked contrast to the

salvarsan dilution or salvarsanized serum we find the motility of the organisms to be greatly diminished in 20 minutes and in one hour the parasites cannot be seen to move at all. The parasite is seen to be swollen, no longer exhibiting its characteristic curves and within 12 hours none can be found in the field with the exception of an occasional one which will appear swollen, distorted and showing no evidence of motility. This then explains why a course of arspenamine injections is not always curative as the young parasites are killed by feeding on the protein sensitized arsenical while the older, more matured types escape to start a new cycle when conditions again become favorable to their growth.

#### CONTROL TESTS

First. A capillary drop of distilled water mixed with a capillary drop of treponema suspension showed only a lessening of motility of the parasites, which is also noted in the suspension alone, starting usually in thirty minutes to one hour from the time of collecting the specimen. However, sluggish motility may be demonstrated in the suspension without the addition of water for five or six days after a specimen is collected provided drying of the preparation is prevented.

Second. In preparing salvarsan an alkaline solution was used. Myers has pointed out that it requires .42 c.c. of normal sodium hydroxide to neutralize .1 gm. of salvarsan and in administering the drug he advises using double this quantity of alkali or .84 c.c. normal sodium hydroxide per .1 gm. of salvarsan. We dissolved this quantity of drug and alkali in 20 c.c. of distilled water in our administration to patients, so in order to test the effect of alkalinity on the spirochete .42 c.c. of normal sodium hydroxide was added to 20 c.c. of distilled water and a capillary drop of this mixed with the spirochete suspension; sluggish motility was demonstrated at the end of twenty-four hour observations.

Third. A suspension of treponema was mixed with a capillary drop of normal serum containing a relatively large number of leucocytes. Active motility was demonstrated at the end of twenty-four hours. This control was used as a serum control and was thought to answer for a tissue extract control.

In contrast to the arsenicals, mercury and its preparations are direct chemical poisons to the treponema as evidenced by the fol-

lowing observations. Mercury bichloride in 1:1000 dilutions inhibits motility in 20 minutes, the spirochetes disappearing entirely from the field within 6 to 12 hours. Mercury benzoate in the dilution of 1:450 inhibits motility within 20 minutes, the spirochetes disappearing in from 12 to 24 hours.

#### SUMMARY

1. Arsphenamine in a dilution of 1:130 does not kill the Spirochete pallida within 12 hours.

2. Nearsphenamine in a dilution of 1:130 does not kill this parasite within 12 hours.

3. Silver-salvarsan in a dilution of 1:125 does not destroy it in 12 hours.

4. Salvarsanized and neosalvarsanized serum from blood drawn at 2 hour intervals after injection for 12, 24, 36 and 48 hours does not kill the treponema.

5. Salvarsanized tissue extract 24 hours after injection kills the treponema in 6 to 12 hours.

6. Salvarsan exerts its action on the Treponema pallidum by combining with the cellular protein producing an arsenoprotein which is detrimental to its growth, starting retrograde changes in the parasite which makes it an easy prey to the protective powers of the body.

7. Mercury and its preparations are direct chemical poisons to the treponema.

## PROPHYLAXIS AND MANAGEMENT OF SYPHILIS

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(Received for publication, March 13, 1922)

**P**ROPHYLAXIS, properly carried on, would in time do away with syphilis. On account of the fact that there has been too little prevention of syphilis, there is no village in the civilized world today that does not have its share of syphilitics. The late crusade against vice by the public health service, aimed at eradicating venereal diseases, although by many stamped "a fiasco," was a step in the right direction. The management of syphilis and gonorrhea in the U. S. Army, especially in France, took on much of the prophylactic aspect and will be partially related here.

I know little of what was done in this line in the United States in the army following December, 1917. My experience in the A. E. F. is, briefly: For eight months I was detachment commander of about 250 medical corps men. There was but one venereal case in the company during that time, and he was imported. The lads were real Americans from all walks of life. They were taught:

- (1) That sexual intercourse was unnecessary to good health;
- (2) That drunkenness and uncleanness were the chief agents in spreading venereal diseases;
- (3) That urinating and thorough washing with soap and water immediately after coitus would protect against chancre, chaneroid and gonorrhea;
- (4) To hurry to a "Prophylaxis station" and receive the regulation "argyrol injection and application of mercury ointment."

The above rules were followed or else there would have been more cases of venereal diseases among the detachment. This experience was in no way unique. To those not acquainted with the bimonthly physical examination in the army, will say that this consisted of a throat, chest, and especially genitalia inspection twice a month by a medical officer. The date of examination was impromptu and varied, the men not knowing when they were to be examined.

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\*Dr. Shuman will leave September 13 for Beirut, Syria, where he has accepted the chair of Internal Medicine in the Medical College of the American University.

A word here about the prophylactic stations in the A. E. F. may not be amiss. These stations were not "hid under a bushel" but placed so that he who ran chances might see and read the sign in red letters "PROPHYLACTIC STATION." The hospital corps men in charge were neither ignorant nor lazy in carrying out their duty day and night. It is also quite true that there was a penalty for the individual developing venereal disease and this penalty was more severe if the unfortunate one had no record of having received prophylactic care.

On account of the foregoing, statistics show that venereal diseases were vastly lower in the U. S. Army than in any other army; also in the late war than in any previous conflict. Those of us who had opportunity to visit the venereal camps of other armies which did not practice prophylaxis and see the large number of men "off duty for six weeks or longer" agreed that the need of venereal prophylaxis is greater than for treatment. However, it is a lamentable fact that many of our soldiers, following "paid in full, and honorably discharged" on this side, contracted syphilis or gonorrhea before getting home! And who is to blame for this? Those who scorn facts and preach but do not believe, that ignorance is bliss and knowledge sinful; that vice should not be restricted and under government control. So long as these emissaries of misery continue to clog the wheels of progress, syphilis and its allies will increase.

Early recognition is the next step in the stamping out of syphilis. The most common lesion confounded with chancre is the chaneroid. Too often the physician is willingly or unwillingly misled by the patient. Recently I examined a young man with one-fourth of the head of his penis sloughed away by a chancre situated in the anterior urethra. He had consulted a physician a month before who without examination diagnosed gonorrhea and advised treatment. This is but an extreme example of carelessness. For this and minor crimes I suggest the following dictum: *Every acute sore, especially about the genitalia, which does not show signs of healing in four days should be regarded as syphilitic.* Suspecting it to be syphilitic let us then use the microscope and serum reaction intelligently. It is most fortunate for the diagnostician that as the spirochete grows more difficult to find in the sore (up to six weeks), the Wassermann reaction becomes more positive (after six weeks).

## CURATIVE TREATMENT

The first aim in treating primary syphilis is to render the individual a safe member of the community so that further spread of the disease will not take place, also to render the person from whom he contracted it likewise. Without going into too much detail it can be safely stated that mercury is a specific for syphilis if properly administered. The greatest error committed is not administering enough of the drug. My preference is  $\text{HgCl}_2$ , in normal salt solution, given intramuscularly in one-fourth to one-half grain doses and often enough to produce a marked mercurial impression. Most of us will agree that small doses of mercury and arsenic are worse than none at all for the reason that the *Spirocheta pallida* becomes tolerant to the drug or drugs, in other words immune. This is manifested in treating the secondary or tertiary lesions of an individual who has had similar but insufficient treatment for the primary lesion, for it is soon noted that the patient is more tolerant to the drug and the lesion heals very slowly.

No doubt we deal with types of syphilis like types of typhoid or pneumonia although not yet so well defined. When we remember that prior to 1905 the spirochete was undiscovered, that since then the serum reaction has been discovered and the old arsenic therapeutics rejuvenated in "Salvarsan" we feel that it is possible that syphilis will be typed before long. There is much clinical evidence that special forms of spirochetes attack certain structures. For example in 1916 I treated a tailor, age thirty-four, suffering with secondary syphilis; he had had his initial lesion three months before; it was indifferently treated. Under mercury and neosalvarsan treatment the skin and mucous membrane lesions quickly disappeared. I treated him diligently the next nine months, at which time he developed aphasia, soon became violent, was admitted to an insane hospital and died two months later from "brain syphilis." Question: Was this virulency of infection, a special type of spirochete, or fertility of soil? It was fertility of soil because when first examined he was anemic, undernourished, sedentary, had a number of abscesses about the roots of his remaining teeth and was a chronic alcoholic; all of which would make for little or no resistance against any infection. That he did have a type of spirochete that had a special predilection for growth in

the central nervous system is plausible. In the same year I examined two brothers suffering from *tabes dorsalis* whose histories stated that they had received their initial sores from the same woman. Instances like the above are not rare.

Following the clearing up of clinical manifestations of the disease over a safe period, five years, often it is a problem to efface syphilis from the patient's mind, he feels (and there are those who give him cause) that every ache, pain, or what not is a voice of the past. These problems must be met and handled on a square basis. The recognition of syphilomania (in doctor as well as patient sometimes) is the chief step in the right direction. Such pernicious teaching "that from individuals who have had syphilis no untainted child can be born" is to be contradicted.

It is highly improbable that a father can transmit the spirochete via the spermatozoa, the average spermatozoon being smaller than the spirochete, unless there exists a granular form of the syphilitic organism, infecting the head of the spermatozoon (certainly unproven). If the mother is infected then it is a different thing for she will transmit the infection to the unborn child directly through the maternal blood stream, the placenta now known not to be a barrier of the pale spirillum. In this connection every prospective mother should receive a routine Wassermann reaction. Proper treatment of a syphilitic mother during pregnancy will undoubtedly result in the birth of a healthy infant. Every infant born of syphilitic parentage, maternal or paternal, should be carefully observed and a serum reaction made as soon after birth as possible and once a month for six times, and twice a year thereafter for two years. If these reactions have been negative and there have been no suspicious clinical symptoms it is safe to feel that the baby has escaped infection.

That the serum reaction is a great aid in the diagnosis and management of syphilis, none will deny, but the clinical diagnosis should take first place. For example, a male, age thirty-two, was admitted to the surgical service of Camp Hospital "27," A. E. F., with the diagnosis of "indolent ulcer on left breast." It was 7 cm. in diameter and contained a deep slough. The blood Wassermann was "strongly negative." There were no signs of healing at the end of one week. He was referred to the medical service and after a consultation the lesion was diagnosed as syphilitic. The



lesion was healed in ten days after starting intramuscular injections of  $\text{HgCl}_2$ . His history was not as negative as his Wassermann for three years before he had had a similar sore on his other breast which healed only after his family physician had given him mercury. The scar was there to prove it! The therapeutic test of our forefathers in medicine should not be neglected. Our students of medicine today are taught too much about short cuts, for example, microscopic, serological, etc., and too little about the teachings of Hutchinson, Romberg, Fournier, et al, in the diagnosis of syphilis.

In conclusion, let us not decry the good that has been or is being obtained in the management of syphilis. Let us, however, honestly observe and impart honest teachings when and where it will do the most good, first to the profession, and second to the public. To eradicate the disease from the face of the earth should be the aim of mankind in general and the syphilographer in particular. Steps which will accomplish this are:

First; prophylaxis, keeping the healthy from being infected.

Second; curing those that have active lesions no matter in what stage but especially the primary and secondary as these spread the disease.

# THE DISTRIBUTION AND EXCRETION OF ARSENIC AFTER INTRAVENOUS ADMINISTRATION OF ARSPHENAMINE IN CHILDREN

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(Received for publication, May 4, 1922)

## CLINICAL MATERIAL AND METHODS

THE patients upon the study of whom this report is based were under treatment for syphilis in the wards of the St. Louis Children's Hospital. In all cases arspenamine was administered in a dosage of 10 mg. per kg. of body weight, employing for injection the arm vein, the jugular, or in rare instances, the longitudinal sinus. Blood for analysis was withdrawn at stated intervals from some other vein, and in certain cases, lumbar puncture was performed one, two or more hours after the injection. Urine specimens were preserved in stoppered bottles in the refrigerator. Stools were washed into large flasks soon after being passed.

For the arsenic determinations, the modified Gutzeit Method, as described by Scott\* was found to be sufficiently accurate. Blood, spinal fluid, tissues and urine were ashed by the Neumann method, using a mixture of sulphuric and nitric acids. The stools were diluted and warmed with hydrochloric acid and potassium chlorate, until only a small white residue remained; the mixture was cooled, made up to volume and filtered. Aliquots were then ashed by the Neumann method. The white residue, nearly arsenic free, was neglected in these determinations.

## ARSENIC IN BLOOD AFTER ARSPHENAMINE

Blood was taken for analysis at 2, 10, 20, 30 minutes and 1, 3, 6, and 24 hours after the injection of arspenamine. A single patient usually served for 4 such determinations after each injection. The analyses were repeated on the same case in a number of instances. The results, given in milligrams of arsenic trioxide, per 100 c.c. of blood, are shown in Table I and in Fig. 1.

\*Scott, W. W.: Standard Methods of Chemical Analysis, New York, 1918, D. VanNost and Co., ed. 2, p. 40.

TABLE I

NAME	2 MIN.	10 MIN.	20 MIN.	30 MIN.	1 HR.	3 HRS.	6 HRS.	24 HRS.
L.J.	( 2.85 ( 2.3 ( 2.8 ( 2.3			.32 .40 .34 .46	.24 .23 .26 .26	.20 .20 .20 .26		.063
B. T.	( 2.3 ( 2.8			.37 .40	.30 .26	.15 .21		
C. A.	( 2.8 ( 1.8 ( 3.09			.53 .41 .80	.22 .40 .43	.22 .17 .21		
F. R.	( 3.5			.44	.18	.11		
E. H.	( 1.8 ( 3.5 ( 2.8			.50 .58 .30	.37 .22 .22	.22 .20 .14		
M. G.	( 3.1 ( 2.2			.44 .23	.22 .18	.18 .10		
E. B.	( 2.3 ( 2.6 ( 2.6 ( 1.6			.54 .60 .60 .38	.195 .19 .16 .17	.16 .20 .20 .10		
F. F.	( 4.3 ( 3.8			.73	.46 .58	.22 .38		
D. W.	( 1.5 ( 3.8 ( 1.5			.64 .40 .30	.37 .17 .18	.18 .14 .10		
M. V.	( 2.8 ( 3.1 ( 3.8 ( 4.5			.40 .70 .50 .52	.28 .34 .20 .50	.20 .14 .18 .10		
H. K.	( 1.8	1.1	.46	.7 .4 .8			.013 .3	
H. K.	( 4.5 ( 3.1 ( 4.1 ( 2.5 ( 2.2	1.3 .9	.34 .30	.70 .84 .55 .27 .18	.39 .41 .46	.20 .36 .30		.049
B.	2.5			.38	.18	.10		
R. B.	3.5			.65	.46	.11		
P. G.	1.2			.5	.16	.08		
R.	1.8	1.0	.61	.38				

TABLE I —CONT'D.

NAME	2 MIN.	10 MIN.	20 MIN.	30 MIN.	1 HR.	3 HRS.	6 HRS.	24 HRS.
R. R.	.9	.9	.07	.07				
M. F.								.01
B. S.								.041
M. L.								.049
L. B.								.009
W. T.								.025
D. T.								.028
V. R.								.013
J. J.	2.7	.6	.24					
No. of observations	38	6	6	38	32	33	2	9
Average mg. per 100 c.c.	2.8	1.32	0.56	0.47	0.303	0.187	0.157	0.034
Per cent	100%	47%	20.1%	16.9%	10.8%	6.7%	5.6%	1.2%

On the whole, there is fair agreement among the figures. In each series, the arsenic content at 2 minutes was designated as "100 per cent," and from this figure the percentage of arsenic present at various times was calculated. The averaged percentage values serve as a basis for Curve I. The most striking result of these de-

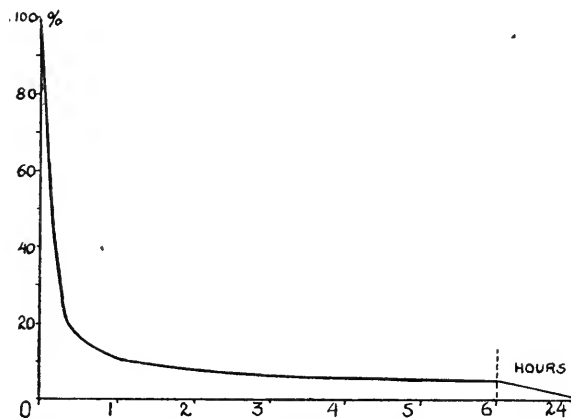


Fig. 1.—The disappearance of arsenic from the circulation after intravenous injection of arsphenamine. The curve shows the percentage of arsenic (as  $\text{As}_2\text{O}_3$  in whole blood) still present.

terminations is the great rapidity with which arsenic at first disappears from the circulation; 50 per cent remaining for 10 minutes, and only 10 per cent at the end of one hour. Since these figures apply to total arsenic and since some of the arsphenamine may have

already been altered, it is obvious that arsphenamine itself may disappear even more rapidly than these results would indicate. After the first hour, the rate of disappearance of arsenic is much slower. This fact is open to various explanations; one of which is that the arsenic is now present in a different form.

A few determinations were made on the same sample of blood, of the arsenic content in whole blood, in plasma and in serum. So far as our methods permit us to say, little or none of the arsenic appears to be present in the corpuscles. This is evident in Table II.

TABLE II

NO.	PLASMA VOLUME IN PER CENT	AS <sub>2</sub> O <sub>3</sub> IN 100 C.C. PLASMA	AS <sub>2</sub> O <sub>3</sub> IN PLASMA OF 100 C.C. BLOOD CALCULATED	AS <sub>2</sub> O <sub>3</sub> IN WHOLE BLOOD AS DIRECTLY DETN'D.
1.	70.5	1.3 mg.	0.92 mg.	1.0 mg.
2.	62.5	0.4 "	0.25 "	0.25 "
3.	69	0.7 "	0.48 "	0.51 "

The arsenic content of serum is equal to that of plasma.

These figures permit us to get some idea of the quantity of arsphenamine introduced into the subarachnoid space by the Swift-Ellis method. In 10 c.c. of serum from blood removed one-half hour after an intravenous injection of arsphenamine, there is about 0.05 mg. As<sub>2</sub>O<sub>3</sub>. If the total quantity of cerebrospinal fluid is taken to be 100 c.c. (or more), the resulting concentration of As<sub>2</sub>O<sub>3</sub> will be 0.005 mg. per 100 c.c. (or less). It will be seen later that the amount of As<sub>2</sub>O<sub>3</sub> which reaches the spinal fluid as a result of intravenous injections alone in infants with syphilis of the central nervous system is 0.037 mg. per 100 c.c. of spinal fluid. The arsphenamine added by the Swift-Ellis method is therefore relatively small. We do not wish to imply that this is necessarily a valid criticism of the method, for the actual treponemacidal activity of the serum and of the spinal fluid probably do not vary simply with their arsenic content.

#### THE DISTRIBUTION OF ARSENIC IN THE BODY

No human material became available for this part of our study. Arsphenamine in the dosage of 10 mg. per kilo was therefore injected into 3 kittens. The results of the analysis of their organs throw considerable light upon the excretion of arsenic observed in

TABLE III  
DISTRIBUTION OF ARSENIC IN BODY OF KITTENS

REMARKS	KITTEN NO. 1. KILLED AFTER 24 HRS. WEIGHT 1200 GMS. DOSE 12 MG. ARSPH.				KITTEN NO. 2. KILLED AFTER 1 HR. WEIGHT 680 GM. DOSE 7 MG. PART OF DOSE EXTRAVASATED				KITTEN NO. 3. KILLED 1 HR. AFTER INJECTION WEIGHT 1075 GM. DOSE 10.7 MG.			
	WT. OF ORGAN	AS <sub>2</sub> O <sub>3</sub> MG. PER 100 GM.	AS <sub>2</sub> O <sub>3</sub> TOTAL MG.	WT. OF ORGAN	AS <sub>2</sub> O <sub>3</sub> MG. PER 100 GM.	AS <sub>2</sub> O <sub>3</sub> TOTAL MG.	WT. OF ORGAN	AS <sub>2</sub> O <sub>3</sub> MG. PER 100 GM.	AS <sub>2</sub> O <sub>3</sub> TOTAL MG.	WT. OF ORGAN	AS <sub>2</sub> O <sub>3</sub> MG. PER 100 GM.	AS <sub>2</sub> O <sub>3</sub> TOTAL MG.
Liver	41.33	.850	.348	47.46	0.78	0.37	27.73	6.8	2.6	27.73	6.8	2.6
Stomach	10.6	.151	.016				9.67	.093	.009			
Duodenum and part of jejunum	3.24	.370	.012				3.13	.45	.014			
Lower Ileum	39.4	.386	.152				32.6	.23	.075			
Rectum and colon	7.37	.380	.028				9.54	.15	.014			
Spleen	2.46	.57	.0135	1.91	.393	.0075	2.21	1.18	.026			
Kidneys	8.26	.154	.0127	6.46	.089	.006	6.9	.56	.039			
Pancreas	4.00	.064	.0025	3.92	.141	.0055	3.26	.245	.008			
Heart	4.54	.0925	.0042	3.51	.125	.004	4.57	.48	.022			
Lungs	7.17	.275	.02	5.04	.037	.002	6.62	.60	.038			
Brain	20.55	.0	.0	22.38	.033	.007	21.74	.016	.003			
Urine	7.33	.341	.025	.0	.0	.0	.....	.....	....			
Skin		1 sq. cm =.0016						1 sq. cm =.00025	....			
Muscle		.0			.0	.0		.0	.05			
Adrenals		.....			....		.16	1.25	.002			
Bone Marrow		.0	.0		.0	.0		.0	.0			

TABLE IV

	INFANTS C.N.S.	INFANTS NO. C.N.S.	LATE C.N.S.	LATE NOT C.N.S.	LATE NORMAL	AVERAGE ALL CASES
<i>1 hour</i>						
No. of pts.	4	2	3	5	2	16
No. of observ.	10	6	11	8	3	38
Average As <sub>2</sub> O <sub>3</sub> mg. per 100 c.c.	.0374	.002	.0184	.012	.019	.0195
<i>2 hours</i>						
No. of pts.	0	2	0	3	1	6
No. of observ.	0	2	0	5	1	8
Average As <sub>2</sub> O <sub>3</sub> per 100 c.c.	-	.0025	-	.016	.02	.013
<i>3 hours</i>						
No. of pts.			4			4
No. of observ.			4			4
Average As <sub>2</sub> O <sub>3</sub> per 100 c.c.			.0048			.0048
<i>4 hours</i>						
No. of pts.				2		2
No. of observ.				3		3
Average As <sub>2</sub> O <sub>3</sub> per 100 c.c.				.0048		.0048
<i>6 hours</i>						
No. of pts.			2			2
No. of observ.			2			2
Average As <sub>2</sub> O <sub>3</sub> per 100 c.c.			.0045			.0045
<i>8 hours</i>						
No. of pts.	1			1		2
No. of observ.	1			1		2
Average As <sub>2</sub> O <sub>3</sub> per 100 c.c.	.0082			.000		.0041

the cerebrospinal fluid, stools and the urine of our human cases. From Table III it is evident that only traces of arsenic are found in the brain, muscles, skin and bone-marrow, but that a considerable amount is present in the liver and intestine, both large and small. As will be seen later, most of the excretion of arsenic is by way of the bowel. It is noteworthy that the heart muscle contains arsenic, whereas none could be demonstrated in skeletal muscle. Arsenic was always found in the lungs. It is a well-known fact that after the injection of acid arsphenamine, the principal part is found as a gelatinous precipitate in the pulmonary capillaries.

#### ARSENIC IN THE CEREBROSPINAL FLUID AFTER ARSPHENAMINE

Our report represents a total of 57 observations on the arsenic content of the cerebrospinal fluid at intervals of from 1 to 8 hours

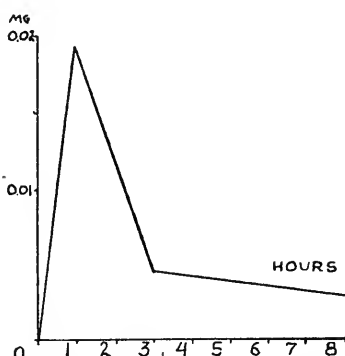


Fig. 2.—Arsenic in cerebrospinal fluid as mgs. of  $\text{As}_2\text{O}_3$  per 100 c.c. at varying intervals after intravenous administration of arsphenamine. The average for all cases.

after the intravenous administration of arsphenamine. These results are summarized in Table IV and the average results are plotted in Fig. 2.

From Table IV and Fig. 2, several deductions may be made. The maximum concentration of arsenic in the cerebrospinal fluid occurs within the first two hours. Considering the rate of disappearance of arsenic from the blood stream the peak of concentration in the cerebrospinal fluid could scarcely occur at a later time. We have no observations to show whether or not the peak is obtained sooner than one hour. It has been our impression from clinical observations that the earlier a child with neurosyphilis is treated the better



the chance of cure and the more quickly is that cure obtained. The laboratory findings here presented seem to explain the clinical observations. Much more arsenic is found in the cerebrospinal fluid of those patients with neurosyphilis than in the case of those with no such involvement. Also much more arsenic is found in infants with neurosyphilis than in older children similarly affected. In some of the infants and older children who had no involvement of the central nervous system (laboratory evidence) no arsenic whatever was found in the cerebrospinal fluid; while the larger amounts were found in those children with the most marked laboratory evidence of inflammation. The smaller amount of arsenic found in the case of the older children with neurosyphilis as compared to the infants indicates the reason for the occasional necessity of intraspinal therapy in older children; while such a procedure is rarely necessary in the case of the infant. The value of 0.018 given in Table IV for the amount found in older children with neurosyphilis is the average for the group. The extremes were 0.002 and 0.03. The smaller value was obtained in the case of a child who had had considerable intravenous treatment without improvement, while the higher value was obtained in the case of a child who did very well with intravenous administration alone. The child with the higher value had a cell count of 187 while the one with the lower value had a count of 50. Our results would indicate that the greater the inflammatory reaction, the greater the penetration of arsenic into the cerebrospinal fluid. We have made no investigation as to whether or not there is an increased permeability after the injection of serum or other material into the subarachnoid space. Several investigators have noted that arsenic is found in the cerebrospinal fluid in decreasing amounts for the same time interval on succeeding injections in the same patient. This is noted also in our material. The cases listed in Table V will serve as examples.

TABLE V

INTERVAL AFTER INJECTION 1 HOUR. FIGURES ARE MG.  $\text{As}_2\text{O}_3$  PER 100 C.C.

CASE B.T.	CASE E.H.	CASE D.W.
3/10 0.008	4/10 0.035	4/10 0.030
3/13 0.005	4/14 0.030	4/14 0.027
3/18 0.000	4/19 0.025	4/19 0.020

TABLE VI  
HOURLY RATE OF EXCRETION OF  $\text{As}_2\text{O}_3$  MIDPOINT OF EACH TIME INTERVAL  
INDICATED

TIME IN HOURS	L. B. 3/25	W. T. 3/25	D. T. 3/25	V. R. 3/25	J. J. 3/29	H. T. 4/9
$\frac{1}{4}$	7.5	0	1.7	1.9		
$\frac{3}{4}$	.67	.13	.54			
$6\frac{1}{2}$	.07		.18		.42	.39
$9\frac{1}{2}$		.03				
13		.03				
$18\frac{1}{2}$			.104	.11	.42	.25
24	.033			.09		
30	.61	.116				
36			.191		.16	.18
42		.03				
44	.133			.09		
60		.168	.39		.04	
68	.28			.10		.19
84		.118				
92	.002			.11	.05	.09
108		.215				
116			.22	.09	.08	.14
132		.103	.14	.16	.04	.09
156		.086	.035	.05		.11
180		.095	.058	.09		.03
204		.078	.01	.05		.07
228		.065	.02	.02		.02
252		.038	.03	.01		.04
276		.016	.005	.02		.04

In order to make results comparable for all cases, the excretion of arsenic as mg. of  $\text{As}_2\text{O}_3$  per hour was divided by the dosage of  $\text{As}_2\text{O}_3$  in mg. and multiplied by 1000. Each curve was separately plotted and the results above recorded were read off from the curve.

#### ARSENIC EXCRETION IN THE URINE

Total urine specimens were collected during  $\frac{1}{2}$ , 1, 3, 12 and 24 hour intervals following the injections of arsphenamine; and as daily total specimens thereafter for 2 weeks or more. We have expressed the excretion of arsenic in two ways; (1) As the total amount excreted at the end of each 24 hour period; (2) As the hourly rate of excretion, for each period. The latter figure is divided by the dose, in order to make results from case to case comparable. This figure will be discussed first. It is obvious from Table VI and Fig. 3 that the rate of excretion is at first very high, as would follow from the high arsenic content of the blood at this time. After dropping to a minimum at 20 to 60 hours, the rate of excretion in all cases but one (HT) rises to a maximum at 55 to

132 hours, after which the level steadily falls. An average curve fails to show this peculiar second rise as clearly as any individual curve, because the maximum falls at different points of time from case to case. As a tentative explanation of this rise, we assume that the rate curve is compound, being made up of two parts: first, the

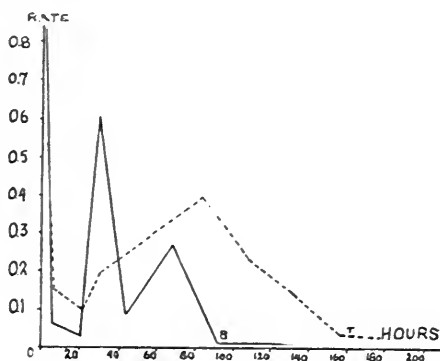


Fig. 3.—Rate of excretion of  $\text{As}_2\text{O}_3$  after intravenous administration of arsphenamine. The rate in mg. per hour, divided by the dose, and multiplied by 1000, is plotted against the time in hours at the mid-point of the intervals during which urine was collected. For clearness, only the 2 curves showing the most striking secondary rises are drawn.

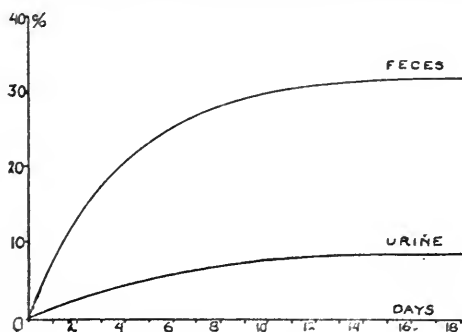


Fig. 4.—Arsenic excretion in urine and feces as percentage of the injected dose, showing the relatively greater excretion in the feces, the slow excretion after 8 or 10 days, and the fact that at the end of 2 weeks about 50 per cent of the arsenic is not yet excreted.

curve expressing the rate of excretion of arsphenamine itself, which rapidly becomes vanishingly small; and second, the curve of excretion of arsenic derivatives slowly split from the deposits of arsphenamine in the tissues. This curve would naturally have a maximum, and would determine the shape of the later arsenic excretion (rate) curve. This hypothesis is under further investigation.

The total arsenic excreted in the urine rises rapidly for 8 or 10

days, then much more slowly. The averaged per cent excreted, based upon our analysis of arsphenamine by the Gutzeit method, is shown in Fig. 4.

#### ARSENIC EXCRETION IN THE FECES

As is seen from Table VII and graphically from Fig. 4, after a single dose, arsenic excretion in the stools is about 5 times as great as in the urine. This is undoubtedly associated with the high arsenic content of the liver and intestinal wall. Both forms of excretion, however, leave unaccounted for more than 50 per cent of the arsenic, which must exist as a very slowly diminishing store in the tissues.

TABLE VII  
EXCRETION OF ARSENIC ( $\text{As}_2\text{O}_3$ , MG.) AFTER ARSPHENAMINE

NAME	V. ROB.	H. T.	W. T.	D. T.	J. J.	D. T.	W. T.
DAY	URINE STOOL	URINE STOOL	URINE STOOL	URINE STOOL	URINE STOOL	URINE STOOL	URINE
1		2.3	0.17	1.1	2.95	1.4	2.8
2	.97	2.6	0.54	2.2	4.1 19.6	2.8	4.0
3	1.3 10.3	5.0 30.6	1.5	2.3	4.3	3.4	7.1
4	1.8	5.7	2.5 25.0	4.5	4.7	4.1	8.5
5	2.1	6.7 39.4	3.7 28.4	5.8 17.3	5.3	4.7	10.1
6	2.7 13.9	7.3	4.3	6.7 20.5	5.5 28.9	4.8	12.3
7	2.9	8.1 39.7	4.8	6.9 21.9		5.1	14.7
8	3.3	8.3 41.5	5.3	7.2 23.6		5.3	14.9
9	3.5	8.8	5.7 31.2	7.2		5.3	15.2
10	3.55 17.7	8.9 42.7	6.3	7.4 25.9		5.4	15.7
11	3.6	9.2 43.3	6.5	7.5 26.6		5.6	11.0
12	3.7 19.3	9.5 43.8	6.6 31.4	7.6 26.9		5.8	11.0
13	3.8 19.6	9.6 44.3	6.7 31.7	7.6 27.4		6.2	11.0
14	3.9 19.9	9.6 44.5	6.8	7.6 27.8		6.3	11.0
15	4.0	10.0 45.0	6.8	7.6			
16	4.0	10.2	6.8	7.7 28.0			
17	4.04 20.3	10.2	6.9				
18	4.07 20.4	10.4	6.9 31.7				
19	4.08 20.7	10.4 45.0	7.2				
20	4.12		7.4				
21	4.14 20.7		7.4				
Per cent excreted							
	6.4 32.0	7.7 37.5	7.9 34.0	7.9 29.0	4.7 24.9	2.3 40.0	5.5
Dose of arsphenamine							
	161 mg.	300 mg.	232 mg.	241 mg.	116 mg.	230 mg. for 3 days	230 mg. for 3 days

Total arsenic excretion as mg. of  $\text{As}_2\text{O}_3$  at end of daily periods, and the excretion in per cent of the injected arsenic, based upon an  $\text{As}_2\text{O}_3$  content of 41 per cent for arsphenamine.

Arsenic excretion after intensive treatment was studied in 2 cases. These received full doses of arsphenamine on 3 successive days. (Table VII; D. T.; W. T.) In both cases it is seen that the urinary excretion of arsenic is relatively much smaller than after a single treatment. In only one case intensively treated was it possible to study the stools. In this case the total excretion was 44 per cent, whereas the excretion following a single treatment had been 37 per cent.

#### SUMMARY AND CONCLUSION

Results are reported of arsenic determinations after intravenous administrations of arsphenamine in standardized dosages in children. The rate of disappearance of arsenic from the blood, the distribution in the body and the rate of excretion are shown.

Arsphenamine rapidly disappears from the blood, but 10 per cent remaining in 1 hour. In the blood it is present exclusively in the plasma. The organs taking up the largest amounts are the liver and the small and large intestine. The excretion begins immediately, is very rapid at first, gradually diminishing until at the end of two weeks only traces are found. However, at the end of 2 or even 3 weeks 50 per cent is still in store in the tissues. It is excreted 5 times as rapidly in the stools as in the urine. The curve of excretion via the urine is a peculiar one and is evidently a composite of 2 curves. It seems likely that the curve of excretion via the stools would be of the same type if the stools could be collected accurately at stated intervals.

The amount of arsenic found in the cerebrospinal fluid is greater in the first hour (in some cases 2 hours) after intravenous administration. The amount of arsenic found in the cerebrospinal fluid seems to depend upon the amount of inflammation present. In some children with no evidence of neurosyphilis no arsenic was found. The greatest amounts were found in those cases with evidence of the most active inflammation. More was found in infants with neurosyphilis than in older children similarly affected. In all patients was noted a diminishing amount of arsenic in the cerebrospinal fluid at succeeding injections and for the same time intervals.

The arsenic content of the spinal fluid is at least as great in cases of cerebrospinal syphilis after intravenous administration of arsphenamine as would result from the intrathecal injection of arsphenamine serum according to the Swift-Ellis technic.

## VALUABLE SUGGESTIONS FOR CONTRIBUTORS TO THE AMERICAN JOURNAL OF SYPHILIS

"The four rules for the preparation of an article will then be: (1) Have something to say; (2) Say it; (3) Stop as soon as you have said it; (4) Give the paper a proper title."<sup>1</sup>

Let your phraseology express one meaning and one only. Be clear.<sup>2</sup>

**Manuscript.**—Manuscripts should be typewritten, with wide margins, and double spaced, on one side of paper 8½ by 11 inches in size. The original copy should be sent to the "Journal" and the carbon copy retained by the author. Number the leaves consecutively, beginning with the title page. Put your name and address on the manuscript.

**Illustrations.**—Illustrations should be clear, preferably pen-and-ink drawings. Of photographs send a good print rather than a negative. Have lettering parallel to the bottom and top margins, and of sufficient size to be clear if cut is to be reduced. Tracings should be in black-and-white; avoid colors. Write your name on back of each picture; number them in one series (Fig. 1, etc.) to the end, and indicate in margin of the manuscript about where each is to be printed. See that the text references and "figures" correspond. Legends for illustrations should be written on a separate sheet.<sup>3</sup>

**Bibliographic References.**—Give only references actually consulted. If an article is known only through an abstract give reference to the abstract in addition to that of the source. References are printed to be of help in further reading; therefore they must be complete, concise, and correct. Follow the style of the "Index Medicus" and "Index-Catalog of the Library of the Surgeon-General's Office." Be conservative in the use of abbreviations.<sup>4</sup>

**Arrangement.**—As authors are quoted in the text give each a number in the order of citation, and number the bibliographic reference with the same number. Arrange the references in a list at the end of the article in the order of the numbers (see below), or arrange items in alphabetical order according to last names of authors, and distinguish between articles by the same author by the use of the date after his name in the text.

**Foot-notes.**—Where an author wishes to use foot-notes at bottom of each page instead of the bibliography at end of article, the foot-notes should be written in the text, but separated from it by horizontal lines above and below, or *better*, place them at bottom of each page. Use figures to indicate these foot-notes, and number consecutively (1, 2, 3, etc.) throughout the article. If in addition to the bibliography mentioned above it is desired to use foot-notes on certain pages, these can be indicated by an asterisk (\*).

**Final Reading.**—Let some one other than the author read the manuscript with these directions in mind.

**Shipment.**—Send manuscript flat, postage paid, to the editor, Dr. Wm. H. Deaderick, Dugan-Stuart Bldg., Hot Springs National Park, Ark.

**Proof-reading.**—Read carefully, with special attention to spelling of names and bibliographic data. Make corrections *in the margin* only with lines drawn from the revision to the point of change in the text. Answer queries in the proof by making correction or crossing out the query. Verify your references from the sources, not from your carbon copy.

### References. (Read these.)

<sup>1</sup>Billings, J. S.: Our Medical Literature, Trans. VII Intern. Med. Congress, Lond., 1881, i, 54-70.

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<sup>3</sup>Suggestions to Medical Authors, issued by the A. M. A. Press, Chic., A. M. A., [1914 (?)].

<sup>4</sup>Place, F.: Bibliographic Style in Medical Literature, Med. Record, N. Y., 1913, lxxxiii, 157-160.

# The American Journal of Syphilis

A QUARTERLY JOURNAL DEVOTED TO THE  
STUDY AND PREVENTION OF SYPHILIS

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VOL. VI.

ST. LOUIS, OCTOBER, 1922

No. 4

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## Original Articles

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### THE TRANSMISSION OF SYPHILIS TO THE SECOND GENERATION

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(Received for publication, June 3, 1922)

IN the examination of a number of children with hereditary syphilis, and their families, there are not infrequently encountered instances in which the infection presents certain apparent vagaries in transmission. These are somewhat more evident when Wassermann tests are carried out on both parents and children. The purpose of this paper is to enumerate and discuss certain of these irregularities or apparent departures from the rule in the transmission of the disease to the second generation which have recently come to our attention. Many of the cases cited were encountered during the course of a study<sup>1</sup> of the incidence of hereditary syphilis in St. Louis while others have been noted in the routine examinations of hospital and dispensary practice. During the past ten years this material has revealed approximately 100 new cases of hereditary syphilis each year. The fact that we have had close supervision over the Wassermann tests, of which 1500 were performed

annually on infants and children, as well as the clinical material, has given us an opportunity to compare rather critically the results of blood tests with clinical examination of the patients. The results have served to strengthen our confidence in the value of the Wassermann reaction in the hereditary form of the disease.

In this paper the diagnosis of syphilis in adults is based upon the history and the Wassermann reaction, while in children it is based upon the physical examination in addition to the history and Wassermann. The Wassermann tests were all supervised by one of us (J. V. C.). Both the alcoholic and cholesterolized antigens were employed with 0.1 c.c. of inactivated serum, using a carefully titrated antisheep hemolytic system described elsewhere.<sup>2</sup> While a discussion of the interpretation of the Wassermann reaction seems unnecessary, it may be stated that complete or nearly complete fixation with the alcoholic noncholesterolized antigen in our opinion means syphilis and is so considered in this paper. Lesser degrees of fixation, as for example, those with the cholesterolized antigen alone, are classed as doubtful reactions, although we realize that in many adults such weak reactions constitute the only serologic evidence in a clinically active syphilitic infection.\* "Strongly Positive" or "4+" when used in describing the tests will be understood to mean complete fixation with both antigens.

#### SYPHILITIC CHILDREN BORN TO MOTHERS WITH A NEGATIVE WASSERMANN

Considerable evidence exists to substantiate the rather general belief that in every instance the mother of a syphilitic child harbors the *Spirocheta pallida*. While it has not been proved that maternal transmission is always preceded by maternal infection, neither are we aware of proof of direct paternal transmission in the absence of maternal infection. It is indeed difficult to believe

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\*It is unfortunate that all reports including Wassermann reactions do not state the technic employed, or at least the antigen used, since certain apparent discrepancies in the clinical and laboratory findings may be due to the methods employed in making the tests. We have sometimes observed positive reactions of varying intensity with cholesterolized antigen alone in children in whom syphilis could be excluded. In many of these instances the reaction was apparently due to some transient blood change since it could not be demonstrated later, as, for example, in certain cases of scarlet fever, although it has occurred in children not suffering from acute infections. In other cases, such a positive reaction with cholesterolized antigen accompanied a strongly positive fixation for tuberculosis and therefore seemed in some manner due to substances resulting from the tuberculous infection. It is rare to observe a positive reaction with the noncholesterolized antigen, however, in a child in whom other corroborative evidence of hereditary syphilis is not obtained when the parents and other children can be examined.



that spirochetes from the father would confine their activity entirely to the ovum and not take lodgment in the maternal tissues also, nor does it seem probable that an ovum so inoculated would develop. The fact that any protection from syphilis without infection has not been demonstrated either in man or experimentally would not support the assumption of the development of an immunity in a nonsyphilitic mother who carries a fetus infected from the sperm. Many mothers of syphilitic infants fail to give evidence of infection either in the history or on examination. One of the most striking features of syphilis is the great tendency for the infection to become clinically latent even without treatment. This latency is obviously due to the development of some tissue immunity in these patients even though the infecting organisms are still present. When pregnancy occurs, the fetus does not share this protection and may be infected if a transient spirochetemia occurs.

In this paper several cases are cited in which the mothers of younger syphilitic children have been free from clinical evidence of syphilis and have also had negative Wassermann reactions. Taken alone such instances might be thought to indicate that these mothers had escaped infection. It must be remembered, however, that these cases have been culled from a rather large mass of material and represent rare exceptions to the usual observation that mothers of syphilitic infants have positive Wassermann reactions. The proportion of such cases observed is considerably less than the proportion of adults with negative Wassermann reactions but with more or less active clinical manifestations of late syphilis.

In a former study<sup>3</sup> one of us showed that 85 per cent of the mothers of syphilitic children gave positive Wassermann reactions. Of the remaining 15 per cent, the infected children, with one exception, were over ten years of age and in some of the families nonsyphilitic children had since been born. That a syphilitic infection may become quiescent in the course of time to such an extent that the serum gives a negative Wassermann reaction, even though spirochetes are still present in the body, is a matter of common knowledge. A negative Wassermann reaction in an untreated syphilitic individual, therefore, indicates an infection merely quiescent but not necessarily extinct. Thus, a negative

Wassermann reaction in the mother of an older syphilitic child is readily explained.

In the course of the present study, similar instances were encountered and several of them will be cited to show that even the mothers of younger syphilitic children may occasionally have negative Wassermann reactions.

CASE 1.—F. H., eight years old, with an interstitial keratitis and 4+ Wassermann. A brother of four years and the mother were clinically well and had negative Wassermann reactions.

CASE 2.—H. Y., six years old, with interstitial keratitis and periostitis. Wassermann 4+. The father gave a history of infection 9 years previously but both his and the mother's blood were negative at the time of examination and also six months later.

CASE 3.—B. C., six and one-half years old, with periostitis, and her sister, H.C., four years old, both gave 4+ Wassermann reactions. The father's blood was also 4+ but the mother's was negative.

CASE 4.—M. C., five years old, with keratitis and 4+ Wassermann. The father gave a history of chancre 13 years previously and had also a strongly positive Wassermann. The mother's blood was negative.

CASE 5.—L. B., two and one-half years old, had condylomata ani and strongly positive Wassermann. The mother's blood gave a 1+ reaction with the cholesterolized antigen only.

One would suppose that an infection quiescent enough to be accompanied by a negative Wassermann reaction would not be sufficiently active to result in the infection of offspring. However, we have recently encountered several instances in which mothers of young syphilitic infants gave negative reactions.

CASE 6.—J. T., three and one-half months old, dactylitis and scaling soles. Wassermann 4+. The mother's blood was 4+ three years previously, and the only treatment that she then received was 4 doses of arsphenamine. Four months before the baby was born her Wassermann was 4+ with cholesterolized antigen only and she was given five mercury injections and one dose of arsphenamine before parturition. At the time the baby was examined, three and a half months later, the mother's Wassermann was negative.

CASE 7.—B. K., at seven weeks of age had a strongly positive Wassermann but showed no clinical signs of the infection. The mother's blood was negative three months before the birth of the infant.

CASE 8.—I. C., five weeks of age had well marked clinical syphilis and a 4+ Wassermann reaction. The mother at this time had a negative reaction.

CASE 9.—H. A., eleven weeks old, had typical syphilitic skin lesions and a strongly positive Wassermann. The mother showed a 1+ reaction with the cholesterolized antigen only.

Such cases are certainly not of common occurrence and in our opinion denote latency of infection in the mother, and not sperm transmission.

#### NONSYPHILITIC CHILDREN BORN TO MOTHERS WITH A POSITIVE WASSERMANN

CASES 10 to 16 comprise four infants examined at two months of age, one at four months, one at five months and one at nine months, all of whom were free from any evidence of syphilis and had negative Wassermans. In each instance the mother's blood was strongly positive.

In this group the mothers were considered syphilitic and the infants nonsyphilitic. Mention will be made later of syphilitic infants who gave negative Wassermann reactions for a short time after birth. On account of the age at which some of these infants were examined it is possible that a few of them might later prove syphilitic, although in this study we have never encountered the appearance of the infection in an infant whose Wassermann was negative at two months of age. The failure of the mother to infect the fetus in some instances may be plausibly explained by the assumption that the maternal infection remained localized during the pregnancy at foci more or less distant from the placental site; or if a transient spirochetemia occurred, the organism did not lodge in the placenta. Our observation has been that if the infection in the mother is sufficiently active to cause a strongly positive Wassermann, the chances are high, more than 70 per cent, that her offspring will be infected. The cases cited, of course, represent exceptions to such a rule. None of the mothers in the group reported had received treatment during pregnancy, or at any time.

#### FATE OF CHILD WHEN MOTHER HAD WEAKLY POSITIVE WASSERMANN

When the mothers of older syphilitic children are tested it is quite common to find the Wassermann reaction positive only with the cholesterolized antigen. Such a reaction would suggest the possibility of the maternal infection being less active than at the time the child was born. In the mother of a syphilitic infant a strongly positive Wassermann is to be expected, although if a

mother with a negative reaction can bear a syphilitic infant, certainly a mother with a weakly positive reaction may also. It is not unusual to observe such cases as the following:

CASE 16.—O. P., an infant, four months of age with rhinitis, typical skin lesions and a strongly positive Wassermann. The mother's reaction was 4+ with the cholesterolized antigen only.

CASE 17.—T. F., an infant examined at three months showed no clinical evidence of syphilis but had a 4+ Wassermann reaction. The mother's blood was 4+ with the cholesterolized antigen only.

CASE 18.—B. G., eight months old, had large epitrochlears and spleen. Wassermann 4+. The mother had received no treatment. Her Wassermann was 2+ with the cholesterolized antigen only.

A mother with a Wassermann positive with the cholesterolized antigen only will usually bear a nonsyphilitic infant. From our own observations such an event is far more frequent (six to eight times) than the bearing of a syphilitic infant. In many of the cases dealt with in this report, a complement-fixation test for tuberculosis was made parallel to the Wassermann test, and it was noted that a slight overlapping sometimes occurred, i.e., a patient with a strongly positive fixation for tuberculosis occasionally gave a positive reaction in the Wassermann test with the cholesterolized antigen only. Such overlapping has occurred in cases in which it seemed certain that no syphilis was present. Had the Wassermann reaction been performed alone or with the cholesterolized antigen alone, an error in judgment or diagnosis would easily have been possible. In fact we have repeatedly observed adults with tuberculosis and a positive complement fixation being treated for syphilis the only evidence of which was a positive Wassermann reaction with cholesterolized antigen. The material of this report includes twelve Wassermann-positive mothers of nonsyphilitic infants. Four of these mothers had a strongly positive Wassermann with cholesterolized antigen, negative with alcoholic antigen and negative fixation for tuberculosis; one had a weakly positive Wassermann with cholesterolized antigen and a negative fixation for tuberculosis; and seven had a positive fixation for tuberculosis and strongly positive Wassermann with the cholesterolized antigen only. One of the latter group had had a negative Wassermann several years previously.

## WASSERMANN REACTIONS ON THE FATHERS OF SYPHILITIC CHILDREN

The presumption is reasonably well founded that in the great majority of instances the syphilitic infection is brought into a family by the adult male member. This may be corroborated by the admission of infection on the part of the father and also to a certain extent by the denial of known infection by the mother. Quite often the father thinks he has been cured before marriage. Despite the presumption that the father is the source of infection, nearly 40 per cent of the fathers of syphilitic children have negative Wassermann reactions at the time the child is brought for examination, frequently when previous infection is admitted. This finding leads to the conclusion that the male may transmit syphilis to the female in spite of the fact that the infection has long been latent and sufficiently inactive to produce no serologic evidence of the disease. Our conception of the mechanism of transmission of syphilis even when latent is based on the observations<sup>4, 5</sup> that in almost all instances the testis is involved. Usually the testicular lesion is accompanied by no clinical manifestations, but is of such a nature that spirochetes occasionally or possibly frequently accompany the semen. Various attempts have been made to demonstrate the organism in the semen and few have been successful. Recently Eberson<sup>7</sup> was able to find them in semen from a latent syphilitic by animal inoculation. In our opinion the difficulty in their demonstration cannot be urged against this method of transmission. The failures are due rather to the scarcity of spirochetes in the semen or the possible inconstancy of their presence and to the small number of experimental inoculations possible from any one individual as compared with the large number of opportunities for inoculation occurring in married life. Case 2 illustrates the not unusual presence of a negative reaction in the father of an older syphilitic child. The following show the same finding in syphilitic infants:

CASE 19.—E. B., eleven months old, with history of snuffles and skin eruption; had a 4+ Wassermann. The mother was not examined but gave a history of having had antisymphilitic treatment. The father admitted gonorrheal infection but denied lues. His Wassermann was negative.

CASE 20.—G. McK., two months of age, had rhinitis and a macular syphilide. The mother, twenty-nine years old, had a healthy nonsyphilitic child nine years of age by a former husband. She gave a history of infection shortly after this

pregnancy and had been treated. Her Wassermann was 4+ with cholesterolized antigen only. The father, twenty-six years old, has a negative Wassermann.

CASE 21.—M. B., seven weeks of age, had a syphilitic epiphysitis which healed with treatment. His Wassermann was 4+. The mother, twenty-six years old, had a Wassermann which was 4+ with cholesterolized antigen only, while the father 30 years old, had a negative reaction.

It is possible that in some instances, e.g., Case 20, the mother was the source of the infection and the father was free from syphilis, and it is sometimes difficult to prove that a father whose Wassermann is negative, has ever been infected. The frequency of observations of latent syphilis in adults who give no serologic evidence of its presence, makes us believe that in the majority of such cases as have been cited, the original source of the disease was the father.

#### TRANSMISSION TO THE THIRD GENERATION

We have never yet encountered an instance in which the proof seemed conclusive that the infection had been transmitted to the third generation. Although it seems highly probable that under most favorable circumstances such transmission occasionally occurs, it is also our opinion that absolute proof of such transmission is practically impossible to obtain. The difficulty is usually that one cannot be sure that the infection was not acquired in the second generation, or that an acquired infection is not superimposed on a former hereditary infection. The following case illustrates well the possibility of such transmission.

CASE 22.—Family F. The father admitted infection before marriage and although the mother had had no clinical evidence of the disease her Wassermann was strongly positive. Five children ranging from 2 to 20 years had also strongly positive Wassermann reactions. In addition there had been three miscarriages and two children who died in infancy. The eldest child, a girl, at 20 years of age developed an interstitial keratitis, a lesion usually associated only with the hereditary form of the disease. Since this girl harbored spirochetes which were able to assume a virulent activity after more than 20 years, it is quite probable that she was able to transmit the disease although no actual transmission was demonstrated.

Usually the offspring of hereditary syphilitic mothers present no clinical or serologic evidence of infection. Sometimes the children of such mothers are mentally or otherwise defective but we have

compiled no data to show that deficiency is more frequent in these children than in those of nonsyphilitic mothers.

#### TRANSMISSION TO TWINS

Many instances of twin births to syphilitic mothers have been recorded. In such reports it is more common for both infants to be infected or for both to escape infection than to have one child infected and the other not. As would be expected from the anatomical relationships, single ovum twins share the same fate, although double ovum twins may not. The most probable explanation is that during a transient spirochetemia of the mother organisms lodging in the single placenta of identical twins infect both; in double ovum twins, on the other hand, with separate placentas and distinct fetal envelopes, the organism may be carried to one placenta without involving the other. In this connection the following two cases may be cited.

CASE 23.—A. A., colored, nineteen years of age, when seven months pregnant was found to have a 4+ Wassermann with the cholesterolized antigen only. She received no treatment. The pregnancy resulted in the birth of twins, a boy and a girl. The girl weighed 2550 grams (5 pounds) and when six days old the Wassermann was 2+ with the cholesterolized antigen only. At three months of age she weighed 4450 grams (9¾ pounds) and had a negative Wassermann. At the age of 13 months her blood was still negative and she had no stigmata of syphilis, although she weighed only 6600 grams (14½ pounds) and had well marked rickets. The boy weighed 1950 grams (4¼ pounds) and when six days old also had a Wassermann which was 2+ with the cholesterolized antigen only. At the age of three months, he was very poorly nourished (3200 gms.) and had snuffles. His Wassermann was 4+ with both antigens. Anti-syphilitic treatment of mercury and arsphenamine was given fairly regularly from the fourth to the tenth month of age and the baby gained very slowly. At the age of 13 months he weighed 5900 gms. (13 pounds) and the Wassermann was still strongly positive. He had no evidence of rickets except slight beading of the ribs.

In the following case of identical twins both infants were infected although the disease presented certain differences in distribution in the two individuals.

CASE 24.—V., twins, both boys, came under observation first at the age of four months. One of the babies had had convulsions and showed a 4+ Wassermann in both the blood and spinal fluid while the other twin had a negative spinal fluid and a strongly positive Wassermann in the blood without clinical signs. Both mother and father had strongly positive Wassermann reactions.

The foregoing case is of interest in connection with the question of whether or not there is a neurotropic strain of the *Spirocheta pallida*. The involvement of the central nervous system in one twin and its escape in the other infant would not lend support to the assumption of such a neurotropic strain. It is not unusual to find that of two or more children with hereditary syphilis in the same family, only one of them has a Wassermann-positive spinal fluid, so that infection of the nervous system probably depends upon other factors than a selective tissue affinity of a certain strain of the organism.

EFFECT OF TREATMENT OF THE SYPHILITIC MOTHER DURING PREGNANCY  
ON INFECTION OF THE INFANT

It is now well established that adequate treatment of a syphilitic mother during pregnancy will result in the birth of a nonsyphilitic infant. We have numerous cases in our material demonstrating this point. It is surprising how little treatment is apparently necessary in some instances to keep the maternal infection in sufficient abeyance to prevent the infection of the infant. One must remember, however, that subsequent pregnancies are not protected unless the treatment of the mother is carried to the point of "cure" or at least continued during each pregnancy. From the social point of view it is also necessary to take the husband into account as a source of reinfection. Since not infrequently syphilitic mothers untreated during pregnancy bear healthy children, it is difficult always to be sure in any specific instance of a mother treated during pregnancy that the treatment itself has prevented the infection of offspring. The exact relation of the treatment, therefore, can only be determined by careful study of a large series of pregnant syphilitic women and we have not sufficient material from which to draw conclusions. Apparently in most cases in which the fetus survives, the infection takes place relatively late in the pregnancy so that frequently treatment of the mother during the latter months results in a nonsyphilitic child. Certain instances may be mentioned, however, in which treatment during pregnancy has been ineffectual in preventing the transmission of the disease. In these it seems likely that the infection of the fetus had taken place before the institution of treatment. It is probable that when a woman contracts syphilis during pregnancy, the infection always involves the placen-



tal site during the spirochetemia which occurs, and the infant is always infected, as in the following instance.

CASE 25.—Mrs. T. P., age nineteen, gave a history of having a genital chancre in March, with secondary eruption in April. Her husband had been infected a year previously. Both had positive Wassermann reactions when seen in May. One dose of arsphenamine and regular bi-weekly injections of mercury were given during May, June and July. The baby, born in August, had clinical syphilis and a strongly positive Wassermann.

Sometimes even in latent syphilis, when treatment by mercury is continued regularly during a considerable part of the pregnancy, the infant is nevertheless born with the disease. An instance in which treatment was more than usually faithful although ineffectual is the following:

CASE 26.—M.C., twenty-three years of age, had had two stillborn children but no other clinical evidence of syphilis. Her Wassermann was positive. In the third month of her next pregnancy, antisyphilitic treatment was begun, consisting of intramuscular injections of from 15 to 20 minims of a one per cent bichloride of mercury solution and an occasional inunction of blue ointment. During the six and one-half months before parturition she received 35 injections always once and occasionally two and three times weekly. The infant, born three weeks after the last treatment, had a strongly positive Wassermann at birth and had a rhinitis and an enlarged spleen.

#### CHANGES IN THE PLACENTA IN SYPHILIS

At one time it seemed probable to us that syphilis in the infant could be determined by microscopic appearance of the placenta. This was investigated and reported in a recent paper.<sup>1</sup> We found that changes sufficiently characteristic and diffuse to be diagnostic were present in the placentas of only 27 per cent of syphilitic infants. In every instance in which the characteristic changes were found, and in which the infant could be examined later, syphilis was present. It appears, therefore, that when these changes are found, they are a reliable index of the presence of syphilis but their absence is of relatively little diagnostic import.

#### THE WASSERMANN REACTION IN INFANCY

Our experience has been that all syphilitic infants give strongly positive Wassermann reactions with the exception of a certain percentage of those in the first few weeks of life who become positive shortly afterward. Indeed, the Wassermann reaction is a much

more constant and reliable index of the presence or absence of syphilis than the physical findings. In a recent survey we found only 50 per cent of infants with strongly positive Wassermann reactions who showed physical evidence of the disease at the time of examination (from two to eight months of age). Furthermore, the reactions on babies at this age are strongly positive, with no partial or weak reactions. Prior to the age of two months certain syphilitic infants may give a negative or a weakly positive reaction. In a recent study<sup>1</sup> we found that of infants later proved to be syphilitic and to have strongly positive Wassermann reactions, 37 per cent gave negative reactions at birth and an additional 18 per cent gave positive reactions with the cholesterolized antigen only. The following three cases illustrate this point, two of them having had a negative Wassermann as late as six weeks after birth.

CASE 27.—J. T., a male infant examined at six weeks of age who was apparently healthy and weighed 11 pounds. His Wassermann was negative. At two and one-half months of age he was still healthy but at three and one-half months of age he was found to have desquamating shiny palms and soles and blood taken at this time was strongly positive. The mother was syphilitic.

CASE 28.—W. P., a male infant who was apparently normal and had a negative Wassermann at the age of six weeks. At three months he developed a dactylitis, and scaling soles. Both the infant and the mother gave strongly positive Wassermann reactions at this time.

CASE 29.—M. M., a girl, was first seen at four weeks of age with occlusion of the nares from a rhinitis which had been present from birth. The Wassermann was negative. At three months of age the rhinitis was still present and the blood showed a strongly positive Wassermann reaction. The mother's Wassermann was 4+ with cholesterolized antigen only.

If a strongly positive Wassermann is obtained at birth or at any other time, syphilis is present. Partial reactions may be encountered at birth or in the first weeks of life and these may be difficult or impossible to interpret. Later observation of the infants shows that in some the reaction becomes strongly positive and in the remainder it becomes entirely negative. This phenomenon is well illustrated in the twin pregnancy of Case 23, in which both infants had weakly positive Wassermann reactions shortly after birth but at three months of age one had become negative and the other strongly positive. That the change in the reaction from negative to positive in the early weeks of life may occur in a syphilitic infant does not appear difficult to conceive, nor does it

seem worthy of comment that during this period varying degrees of positive reactions may be obtained. Of more interest are the nonsyphilitic infants who have weakly positive reactions early in life which later become negative. In all such instances observed by us the Wassermann of the mother was of equal or greater intensity than that of the infant. The conclusion seems unavoidable that in these cases there occurs a transference of the fixing substances from the serum of the mother to that of the infant without the transmission of the infection itself. The fixing bodies thus transferred disappear from the infant's circulation more or less rapidly. This conclusion is borne out by a similar observation made in connection with the complement-fixing substances in tuberculosis.<sup>7</sup> When a mother has a strongly-positive fixation for tuberculosis, the fixing bodies may be transmitted to the offspring, and may be demonstrated in the infant's blood for several weeks after birth although the infant has no tuberculosis.

#### THE WASSERMANN REACTION IN OLDER CHILDREN

In the presence of active manifestations of syphilis in older children and prior to treatment, the Wassermann reaction is strongly positive in almost 100 per cent. We formerly believed that the reaction was positive in fully 100 per cent, but several cases have presented themselves which have made us reluctantly admit the possibility of certain exceptions. Even yet since the examination of a large material with this point in mind over a number of years, has revealed such cases so rarely, we feel that only the most conclusive evidence justifies the diagnosis of an active hereditary syphilis in the presence of a negative Wassermann. The following cases are the only available examples we can cite of older children with signs of hereditary syphilis and a negative Wassermann reaction:

CASE 30.—H. F., a boy, nine years of age, when first seen had an interstitial keratitis, typical Hutchinson teeth, and was deaf. His Wassermann was negative then, also at eleven years (after "provocative" neosalvarsan) and again at fourteen years. The parents were not examined, but two brothers, one seven years younger and one three years younger had negative Wassermann reactions.

CASE 31.—E. B., a girl, ten years old, had cloudy cornea from an interstitial keratitis four years previously. Her upper central incisors were dwarfed and pegged but not notched, and there was an enamel defect of one canine. She also had a nerve deafness. Both parents gave strongly-positive Wassermann

reactions, the father having a perforated nasal septum and the mother being diagnosed as deafness from syphilis of the internal ear. Two older children were negative, and the mother dated her own infection from a period just preceding the birth of the patient. The patient's Wassermann was negative in the spinal fluid but in the serum was a 2+ with the cholesterolized antigen only in Oct. 1918. She received intensive antisypilitic treatment for two years following. In July 1919, the reaction was still 2+ with cholesterolized antigen but in July, 1920, January, May and August, 1921, it was negative.

CASE 32.—E. C., a girl, twelve years old, had marked enamel defects of the teeth involving both the upper and lower incisors and several molars as well. Her Wassermann reaction was 1+ with cholesterolized antigen only, and the spinal fluid was negative. An ocular inflammation six years previously had left bilateral superficial and deep corneal nebulae suggesting an old interstitial keratitis or phlyctenular disease, and she was deaf, the diagnosis being nerve deafness of the type seen in syphilis. The mother's Wassermann was 4+ with the cholesterolized antigen only. Two still-births (seven months pregnancies) had preceded the birth of the patient. A brother one year younger, otherwise well, had extensive enamel changes similar to those of the patient and a strongly positive Wassermann. A younger boy 4 years old had a negative reaction. The father was not examined.

It is of considerable interest that three cases are the only ones we have observed that approach the classical Hutchinson's triad of keratitis, pegged and notched upper central incisors, and nerve deafness. The association of these lesions is, in our experience, very infrequent, although the combination of keratitis and enamel changes in the teeth is not unusual. In Case 30 the keratitis was apparently active at the time of the first examination and negative Wassermann (nine years of age), while in Cases 31 and 32 the corneal lesions had been inactive for several years, although the blood showed a suggestive result (weak fixation with cholesterolized antigen only). The tendency in many syphilitic individuals for the infection to quiet down even without treatment so that the blood Wassermann becomes negative, is seen rather frequently in adults with either the hereditary or acquired form of the disease. In the period of childhood, however, such latency insofar as the Wassermann reaction is concerned, is extremely rare. We have assumed that this may be due to the severity and extent of the infection at a period when resistance is notoriously feeble, and to the time usually necessary for such latency to be acquired. The majority of cases of parenchymatous keratitis give strongly positive Wassermann reactions which are extremely persistent either

with or without treatment, and for one to be encountered occasionally with a different behavior is worthy of note. Because they are so exceptional it might be questioned that they are syphilitic in origin. We have also encountered cases of interstitial keratitis in children in whom we have felt that syphilis could be excluded from clinical and blood examinations of both of the patients and their families. In at least two of such instances the patients have been infected with tuberculosis. However, we cannot state with absolute certainty that occasionally cases of syphilitic keratitis with negative Wassermann reactions may not occur. The possibility may be suggested that in such instances the cornea being itself almost without a blood supply there is not sufficient activity of spirochetes elsewhere to incite fixing substances in the serum. Aside from these possible cases of keratitis, we have never seen clinically active syphilis in older children unless accompanied by a strongly positive Wassermann reaction. Indeed, we have from time to time spent a considerable amount of study on infants and children with certain lesions strongly suggestive of a syphilitic etiology but with negative Wassermann reactions. In almost every instance, however, further investigation of the patient and his family has compelled us to abandon the diagnosis of syphilis. We do not, therefore, share the view expressed by some, that a negative Wassermann has little value in excluding hereditary syphilis in children, at least insofar as syphilitic disease is concerned. In our experience a negative Wassermann in children is quite comparable in diagnostic value to a positive reaction. In adults, on the other hand, a negative Wassermann reaction is relatively common in definitely syphilitic individuals, and is of much less diagnostic importance.

#### SUMMARY

It is highly probable that all mothers of syphilitic children are infected, although occasionally mothers of syphilitic infants have negative Wassermann reactions, and more often mothers of older syphilitic children have weakly positive or negative reactions. In all such instances the maternal infection is latent. A strongly positive Wassermann reaction in the mother does not mean that her infant will necessarily be infected and consequently a syphilitic mother may bear a healthy child. When the mother's Was-

sermann reaction is positive with the cholesterolized antigen only, the chances are about seven to one that the infant is not syphilitic.

In most instances the father brings the infection into a family, although nearly 40 per cent of the fathers of syphilitic children have negative Wassermann reactions (at the time the children are examined). The male may therefore transmit the disease after his infection has become latent. Transmission to the third generation is possible, but is incapable of proof.

Identical or single ovum twins born to a syphilitic mother are both infected or both escape the disease; double ovum twins, on the other hand, have the same fate as children of two successive pregnancies, i.e., either, neither, or both may be infected.

Adequate treatment of the syphilitic mother during pregnancy will result in a nonsyphilitic infant if the treatment is instituted before the fetus is infected. Often a relatively small amount of treatment is necessary to accomplish this. Subsequent pregnancies are not protected unless treatment is continued. It is probable that when a mother becomes infected during the pregnancy the fetus is infected also, but the treatment of the mother may be followed by a milder infection in the infant and lessen the danger of a fatal infection in utero.

Placentas of syphilitic infants show characteristic diffuse microscopic changes in 27 per cent of cases. When such changes are present the infant later proves syphilitic in every instance.

Syphilitic infants at birth have Wassermann reactions in the following proportion: 37 per cent negative, 18 per cent weakly positive and 45 per cent strongly positive. After the first few weeks or months all syphilitic infants have strongly positive Wassermann reactions. Syphilitic infants over two months of age fail to show clinical evidence of the disease at one examination in 50 per cent of instances.

Nonsyphilitic infants may give weakly positive Wassermann reactions at birth which become negative later, but never give strongly positive reactions at birth or any other time. All mothers of such nonsyphilitic infants as give weakly positive Wassermann reactions have themselves reactions of equal or greater intensity than their infants. In these instances the fixing substances are probably transmitted from the mother to the infant without transmitting the infection.

Hutchinson's triad of interstitial keratitis, enamel defects of the upper central incisors, and nerve deafness are rare.

In older children with active manifestations of syphilis the Wassermann reaction is positive in almost 100 per cent. Certain possible exceptions are noted all of whom had keratitis. A diagnosis of active hereditary syphilis in a child with a negative Wassermann reaction is justifiable only when the clinical evidence of the disease is absolute and unmistakable.

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## PRACTICAL OBSERVATIONS ON SYPHILIS. IV

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(Received for publication, September 4, 1922)

### Section 15

#### SYPHILIS OF THE NERVOUS SYSTEM

##### HISTORY

**H**ISTORY.—In 1497 Leoncino described hemiplegia due to syphilis, and in 1530 Paracelsus described syphilitic meningitis. Willis, in 1672, wrote the first authentic description of general paresis. The modern study of neurosyphilis really begins with Heubner's studies on syphilitic changes of the blood vessels in the brain. In 1875, Fournier first stated that syphilis is the only cause of tabes. Within the past ten years there have been a number of advances. In 1913, Noguchi and Moore found treponema in parietic brains and still later Wile proved that rabbits could be inoculated with cerebral tissue removed from a parietic. The use of spinal puncture and treatment by the intraspinal route have been of utmost importance from a practical standpoint.

##### FREQUENCY

Examination of the spinal fluid shows that about 25 per cent of syphilitics have some central nervous involvement during the early stages of the disease. From the clinical standpoint from 8 to 10 per cent of all syphilitic patients show a definite involvement of the nervous system. It is usually stated that 1.5 per cent of the cases of organic disease of the nervous system are due to syphilis, but the author feels sure that the true figures are very much higher and that 5 per cent would probably be a more just estimate.

##### ECONOMIC IMPORTANCE

From the pure dollars and cents aspects, it is probable that the cost of insanity due to syphilis is one-half billion dollars a year. This figure is taken from Stokes' admirable pamphlet entitled "Today's World Problem in Disease Prevention." Further it



should be remembered that insanity constitutes but a small percentage of the cases of nervous syphilis and it is probable that the total bill would be well over two billion dollars annually. Surely we must sympathize with the efforts of the syphilologists, efforts led by Dr. J. A. Fordyce, of New York City, to prevent this complication from arising.

#### ETIOLOGY

There have been many theories regarding the causation of syphilitic infection of the nervous system. It is a well-known fact that even when drugs are administered intravenously they but rarely can be demonstrated in the cerebrospinal fluid. It is also well known that even in the event of septicemia, microorganisms can be found in the fluid in a comparatively small percentage of cases. Both of these facts are explained by assuming that the choroid plexus acts as a filter.

The physiology of the cerebral spinal fluid can conveniently be discussed now. It should be clearly understood that we know much too little concerning this subject. The fluid is believed to be obtained from three main sources; as a secretion from the choroid plexus, as a transudate into the subarachnoid and subdural cavities, and from the intraadventitial lymph spaces of the cortex. It forms a water bed on which rests the base of the middle and posterior parts of the brain and is invaluable as a mechanical protective agent.

Among various causations which have been mentioned but which have been discarded, are the use of alcohol, trauma, heredity, and intellectual strain. Women seem to suffer rather less often than men, but the difference is very slight.

The age of the patient probably plays but little part, and likewise the time of infection is not important. It has been believed that some races suffer much less frequently than others. For instance, the Arabs are supposed to have nervous syphilis very infrequently, but I am not aware of a systematic study by modern diagnostic methods in this race. It should be remembered that a few years ago it was commonly stated that negroes are but rarely affected by cerebrospinal syphilis, a statement which is totally false.

At the present time three theories may be mentioned; first, that the disease is due to a special strain of infecting organism,

second, that it is due to too little treatment, and third, that it is due to too intensive treatment in the early stages, treatment which prevents the formation of antibodies.

Reasoner's work has definitely shown that various strains of the treponema will produce different types of lesions in infected rabbits. White has shown that patients who later have involvement of the nervous system are almost invariably the ones who have had few skin lesions. Another argument is the presence of conjugal tabes or paresis. Finally, there are a large number of cases upon record where a number of persons infected from the same source have developed cerebrospinal syphilis.

Many syphilologists believe that the cases which later develop cerebrospinal syphilis are the ones which have received but little treatment early in the course of the disease. The modern syphilologist is inclined to feel that if a patient has very vigorous, long continued treatment in the early stages of the disease, he is not apt to later develop cerebrospinal syphilis.

At the same time notice should be taken of the fact that certain physicians now believe that the attempt to produce an abortive cure results in the almost—but not complete—sterilization of the body, and that as the result of this the natural defensive reactions of the host are not called into play and hence the nervous system is more liable to infection. This point is certainly not proven.

It is a well-known fact that many patients have suffered from nervous relapses following the injection of a few doses of arsphenamine. However, these cases almost invariably clear up in further intravenous treatment. This phenomenon is usually known as a "neurorezidive."

One factor which is not mentioned in the literature, but which deserves consideration, is the filtrability of the choroid plexus; it seems possible that infecting organism may pass through the plexus much more readily in some individuals than in others.

Examination of the spinal fluid has definitely revealed the fact that infection of the nervous system almost invariably takes place at the time of the septicemia. Stokes, in a personal communication, informs me that so far as he can judge from his work at the Mayo Clinic, not more than 3 per cent of the cases which early show a negative spinal fluid finding, later show a positive finding. In other words, in about 97 per cent of all cases of cerebrospinal

syphilis, the involvement takes place during the first few weeks of the disease. This is a matter of great importance for it means that if a patient gives neither clinical nor laboratory evidence of cerebrospinal syphilis during the very early stages, it is improbable that he will have later trouble.

#### PATHOLOGY

The pathology of cerebrospinal syphilis is identical with that of syphilis elsewhere. The blood vessels show the same characteristic changes that they do in other organs of the body. In addition to the vascular changes, which may be found in the meninges, or more rarely in the brain substance, certain finer changes in the cells have also been described in the parenchymatous types of the disease. The cerebrospinal fluid usually shows an increase in the cell count, a positive Wassermann reaction, and increase in globulin and certain other changes which will be described later.

#### GENERAL SYMPTOMATOLOGY

Naturally the symptoms depend upon the portion of the brain which is involved. The following is a list of symptoms for which we must always look:

Eyes: flattening of the pupils, inequality in the pupils, very small or very large pupils, abnormal reactions to light or accommodation, paralysis of one of the eye muscles, optic inflammation and atrophy.

Ears: sudden deafness.

Local paralysis: hemiplegia, paraplegia, paralysis of the eye muscles, paralysis of the facial nerve and more rarely paralysis of some other nerve or nerves.

Abnormal movements: the stamping gait of tabes, inability to walk in the dark, a positive Romberg, local or general tremors, incoordination.

Changes in reflexes: exaggerated, absent or unequal reflexes, particularly the patellar, tendo Achilles, elbow, or abdominal muscle.

Changes in sensation, headache, increased or decreased susceptibility to touch, heat and cold.

Bladder symptoms: difficulty in voiding, partial retention.

## CLINICAL TYPES

The following classification, a slight modification of that of For-dyce's, can conveniently be made:

1. Parenchymatous
  - tabes
  - paresis
  - tabo-paresis
2. Vascular
3. Meningeal
  - convexity
  - base
  - diffuse cerebrospinal
4. Gumma
5. Peripheral nerves
6. Neuroses

## DIAGNOSIS

The diagnosis of cerebrospinal syphilis cannot always be made with ease. While it is true that an examination of the spinal fluid will yield positive results in about 97 per cent of the cases, still it must be remembered that in certain other diseases an increase in the cell count, or an increased protein content may be found, hence, it is always necessary to interpret laboratory findings with care. In general, we may say that there are four methods of diagnosis; history, symptoms, physical signs, and laboratory findings.

The history is like any other history given by a syphilitic patient, it must always be mixed with common sense. However, treatment for cerebrospinal syphilis at the hands of a competent syphilologist, or neurologist is fairly definite. The history of headaches during the acute eruptive period, or of the later paralysis of the eye muscles is suggestive. In taking the history we must always enquire as to the eye sight, hearing, ability to walk in the dark, and as to any difficulty in voiding urine. Any difficulty along these lines should suggest the possibility of cerebrospinal syphilis.

In examining a patient a definite routine must be carried out. If one picks up a modern textbook upon neurology, he will soon learn that a complete neurologic examination may require months

to perform, but an examination for syphilis can be done rather promptly. It is convenient to first examine the eyes. Here we must look for flattening of the pupils, for any inequality, or for abnormalities in size. Very small pupils are much more suggestive than are large ones. Abnormal reactions to light or accommodation are important, and the same thing may be said of paralysis of one of the eye muscles, or optic inflammation, or atrophy as determined by the ophthalmoscope. It should be especially noted that either flattening or inequality of the pupils does not necessarily indicate any organic nervous trouble. We have had the spinal fluid of a number of patients who present these abnormalities examined, and found nothing.

The hearing should always be tested, and the cause of any deafness determined.

Any paralysis should be noted.

Patient's gait should be studied; the stamping gait of tabes is characteristic. The Romberg should always be tried. Tremors may be searched for by examining the tongue, or the extended arms and hands with the fingers spread apart.

Incoordination can be tested by making the patient close his eyes and *slowly* touch the end of his nose with his forefinger, this being done from as great a distance as possible.

Changes in the reflexes must always be looked for. As a routine the following should be examined; the elbow, the abdominal, the cremasteric, the patellar, and the tendo Achilles. Again it should be noted that the absence of any kicks does not necessarily mean syphilis. Also a patient may show some inequality in reflexes as the result of an old head injury.

Changes in sensation are most apt to be found in the legs. The sensation of heat and cold can conveniently be tested by test tubes filled with hot and cold water.

Examination of the eye ground by an oculist familiar with syphilis is extremely important; in exceptional instances that may be the only finding, either clinical or laboratory, that will give the diagnosis. At the same time more than one patient has had a faulty diagnosis made through careless work.

Cystoscopy may reveal a trabeculated bladder which is also diagnostic of an oncoming lesion, usually tabes. But again, it must be

remembered that other diseases of the cord may produce the same bladder signs.

The laboratory affords much the best means for making an absolute diagnosis of cerebrospinal syphilis. About 97 per cent of all cases show changes in the cerebrospinal fluid. The finding of a persistent positive blood Wassermann which may change slightly under treatment always leads us to *suspect* infection of the nervous system, but is by no means definite.

The examination of the cerebrospinal fluid is the most important part of the laboratory diagnosis. The fluid must be obtained by lumbar puncture, and this involves certain inconveniences to the patient. In common with most syphilologists I am absolutely opposed to the withdrawal of spinal fluid in the office or in the clinic. In the past the majority of men have advised that a patient should be confined to bed for twenty-four hours following puncture, but I consider that fifty-six hours is a much safer time. Patients are advised to go to the hospital on Friday afternoon, are punctured that evening and are kept in bed until Monday morning. It should be borne in mind that a patient who shows increased pressure of the fluid is much less apt to have headache than is a patient who has a normal pressure. Patients are advised to stay in bed simply to obviate the possibility, or probability, of severe headache. The statements of some men that they have never encountered headache after lumbar puncture is to be regarded with grave suspicion. Serious accidents following lumbar puncture are uncommon but can occur. I have seen one case of staphylococcus infection of the meninges. Exceptionally, some hysterical condition may follow; this is very unusual. Patients may be punctured either in the hospital or at home. Every clinic should have facilities for hospitalizing patients for this important procedure.

In performing a puncture the patient is put in a lateral recumbent position, usually lying on the left side and well bent forward. No anesthetic is necessary, although the skin may be frozen with ethyl chloride, or a drop of novocaine injected. The operation itself must be carried on under absolutely aseptic precautions. The best needle is at least 12 centimeters long, of 17 or 18 gauge and very sharp. The needle is introduced just below the fourth lumbar spine. This spine it will be remembered is on a line with highest parts of the iliac crests. The puncture is not made in the

median line, but about one centimeter to the side and is directed inward and slightly upward. It passes through the skin, subcutaneous tissue, spinal muscle, ligamentum flavum, and arachnoid. At a distance from six to eight centimeters the resistance to the needle ceases and the operator "feels" that it is in the subarachnoid space. The stilet is withdrawn from the needle and the fluid allowed to escape into a sterile tube. Six c.c. should be collected. If the fluid escapes with a spurt it can usually be assumed that the pressure is increased, but this is of little diagnostic value.

Examination of the spinal fluid should comprise four tests; first, the Wassermann done upon various dilutions of the fluid; second, a count of the cells present; third, a test for the presence of globulin; fourth, examination for the gold chloride reaction.

The Wassermann reaction in the spinal fluid is performed as upon blood serum. It is usually performed upon varying amounts of serum. The following amount can be conveniently used: 0.5 c.c., 1.0 c.c. and 2 c.c. It is very important to perform the test upon the larger quantity as a Wassermann reaction is frequently present with this amount of fluid, although negative with the smaller amount. A positive serum Wassermann is found only in cases of cerebrospinal syphilis.

The Wassermann reaction in the spinal fluid (first demonstrated by Plaut and Wassermann) is nearly always positive in general paresis, but rare in tabes and cerebrospinal lues unless large quantities of the fluid are used. Nonne, in his second edition (1916) has summed up the "four reactions" admirably as follows:

*General Paresis or Taboparesis.*—

1. Wassermann reaction in the blood positive (nearly 100 per cent).
2. Phase 1 (Nonne and Apelt's method of estimating an increase of globulin by ammonium sulphate), reaction positive (95 to 100 per cent).
3. Lymphocytosis marked (95 per cent).
4. Wassermann reaction in the fluid positive (using 2 c.c., 90 per cent; using larger quantities, 100 per cent).

*Tabes (without combination with paresis).*—

1. Wassermann reaction with blood serum positive (70 per cent).
2. Phase 1, reaction positive (95 per cent); usually strong.

3. Pleocytosis (90 to 95 per cent) usually strong.
4. Wassermann reaction in the spinal fluid (using 2 c.c., positive in about 20 per cent; larger quantities, almost 100 per cent).

*Cerebrospinal Lues.*—

1. Wassermann reaction in blood serum positive (70 to 80 per cent).
2. Phase 1, reaction usually positive, but not so strong as in paresis or tabes; exceptionally negative.
3. Pleocytosis, almost always positive, but not so marked as in paresis and tabes.

4. Wassermann reaction in spinal fluid (using 2 c.c., positive in about 20 per cent; large quantities of fluid, almost always positive).

The above table can be taken as a convenient diagnostic one for the general practitioner to use, but a little more detail about the diagnostic criteria involved may serve to make the subject somewhat clearer. The Wassermann in the blood serum has already been discussed. The Wassermann in the spinal fluid is a very important diagnostic method inasmuch as it is nearly always positive in syphilis of the nervous system and always negative in syphilis without nervous involvement.

An increase of lymphocytes in the fluid is important being present in about 95 per cent of all forms of cerebrospinal syphilis. The more acute the condition the larger the number of cells present. The cells can be counted by either the Fuchs-Rosenthal counting chamber, or by the Alzheimer method. Normally a count of less than five cells per cubic millimeter is considered normal, and more than ten pathologic. An increase in the number of cells may be found in any meningeal infection as well as in certain other nervous diseases such as multiple sclerosis.

An increase of the protein, or globulin content is considered pathologic and the simplest method of estimating this is by the method of Nonne and Apelt—the so-called “Phase 1.” One c.c. of spinal fluid is added to the same amount of a hot saturated solution of ammonium sulphate which has been allowed to cool. One of these liquids is poured gently on the top of the other and if there is an increase of the globulin content a gray ring appears at the line of contact. Then the liquids are shaken together and observed after three minutes. If the resulting mixture is cloudy, the reaction is



positive. The protein increase may also be found in the same conditions that give rise to an increase cell count.

A test which has obtained great popularity in the last few years is the gold sol reaction, commonly known as the Lange colloidal gold curve. The principle of this reaction depends upon the precipitation of gold out of a colloidal gold solution by the changing ratio of protein content. This test should be performed only by an expert laboratory man, and probably the most satisfactory account of the technic is contained in an article by Miller and Levy in the Bulletin of the Johns Hopkins Hospital for May, 1914.

In general paresis the first few tubes show complete reduction, the next few partial reductions, and the reaction tapers down to none at all in the last few tubes. Thus a typical parietic curve would be something like this: 5554432100. A typical cerebrospinal lues curve would be 1133210000.

It is now generally believed that a parietic curve usually, but not necessarily, indicates paresis and hence it is of considerable prognostic importance.

#### PROPHYLAXIS

*Prophylaxis.*—The prophylaxis of cerebrospinal syphilis may be conveniently discussed under three headings; first, the general prophylaxis of syphilis, second, the early diagnosis of cerebrospinal syphilis involvement by means of lumbar puncture; and third, the long continued treatment of syphilis during its early stages.

The general prophylaxis of syphilis need not detain us now as it will be dealt with in a separate section.

Every syphilitic without exception should have a spinal fluid examination during the first year of the disease, for, as has already been emphasized, the involvement of the nervous system takes place during the first few weeks of the disease. The exact time of performing lumbar puncture is possibly open to argument. Fordyce and Stokes both believe that it is best done before the second course of arsphenamine is given. In my practice I have rarely punctured a patient suffering from early syphilis in less than six months after treatment was begun. However, in any case which presented headaches or other signs of cerebrospinal involve-

ment, I have insisted upon immediate puncture. However, I am more and more inclined to feel that an earlier puncture is desirable in many cases. In case a patient shows positive findings in the spinal fluid, treatment must be more intensive and longer drawn out than cases which show a normal fluid. Treatment, possibly including spinal injections must be continued until the fluid is normal. Fordyce deserves special commendation for his efforts in behalf of this measure. If all cases of early syphilis were thus handled we should have practically no late cases of syphilis or neurosyphilis. *Any patient who is treated without spinal puncture is badly treated.*

All cases of early syphilis should probably be treated for at least eighteen months. There should be alternating courses of arsphenamine and mercury with short rest periods during the latter part of the course. If all patients were thus handled it is probable that the nervous system involvement would be much reduced in frequency.

#### TREATMENT

*Treatment.*—The treatment of cerebrospinal syphilis often presents very considerable difficulty and cause for the exercise of judgment in many cases. It cannot be too strongly emphasized that each case must be treated upon its own merits, and that the amount of treatment and the intervals between treatment must be graded according to the peculiarities of the patient and of his disease. Let us always remember that we are treating the patient rather than the disease itself and that no hard and fast rule is applicable in all cases. The following account of the treatment of cerebrospinal syphilis is to be read in the light of the previous remarks and it is intended more as an outline and as a suggestion for treatment from which many deviations must necessarily be made.

The general treatment of cerebrospinal syphilis is that of syphilis of any other portion of the body. However, a patient suffering from this form of the disease is not a menace to society at large in the sense that he is apt to communicate the disease to any others. At the same time it should be remembered that patients suffering from even a late tabes have been known to infect their wives. Hence it follows that the only precaution to be taken

is the limitation of sexual intercourse. Naturally any syphilitic must have the proper food, proper exercise, proper periods of work and rest, and avoidance of mental strain and confidence in the physician who is treating him. It cannot be emphasized too strongly that syphilis is a disease which depresses many of its victims, giving rise to a feeling of inferiority. Even the laity now know that syphilis of the nervous system is serious and a patient suffering from this malady should be able to feel that he is in thoroughly competent hands, and that another is helping him carry his burden.

Mercury is believed by many authors to be of considerable value in the treatment of cerebrospinal syphilis when combined with arsphenamine. Before the introduction of arsphenamine I recall having seen several very striking cases in which the intramuscular injection of mercury produced marked beneficial effects. At the present time, however, the great tendency upon the part of syphilologists is to depend more and more upon arsphenamine. The administration of mercury in neurosyphilis differs in no respect from its use in other forms of the disease. This will be discussed at a later date.

If one should happen to read a text book upon neurology that was written some twenty years ago he would find that the use of iodides in syphilis of the nervous system was extolled; he would also find much discussion as to the dosage, some authorities recommending the usual ten to fifteen grains, three times a day; and others stating that enormous doses, often one ounce and more a day are necessary. At the present time the iodides are but little used. Stokes believes that they are of considerable value in the early cases of meningitis. It is interesting to note that in some late work from his clinic it has been proved that the iodides should be given before meals rather than after meals, as has always been the custom.

Arsphenamine, when given by the intravenous route, can but rarely be demonstrated in the cerebrospinal fluid. Nevertheless even when thus administered it frequently exerts a most beneficial action upon almost any type of nervous syphilis with the exception of general paresis. When we consider that paresis is primarily a parenchymatous disease, and that many of the blood vessels of the cerebrum are involved this failure has always seemed to me

to be striking and rather difficult of explanation. Practically all conservative syphilologists are agreed that in the ordinary cases of cerebrospinal syphilis a thorough course of intravenous medication should first be given. Of course, a spinal fluid examination should be performed before such treatment is begun as otherwise the physician will be working in the dark and it will be impossible for him to say whether or not he is improving the condition. In the ordinary case it is usual to give a course of twelve intravenous arsphenamine injections at intervals of from five to seven days. Then the patient is put upon mercury and at the end of two weeks a spinal fluid examination is again made. If this is found improved, arsphenamine is again administered. The intensity of the second course necessarily depends upon the amount of improvement that has occurred during the first course. If a patient is first seen with a fulminating nervous syphilis, if the laboratory findings do not improve under intravenous administration, if the clinical symptoms do not improve, or if it is impossible to give intravenous treatments, the intraspinal route must be selected.

The administration of arsphenamine intravenously is essentially the same in neurosyphilis as it is in any other form of syphilis. The intervals between doses varies considerably in the hands of different men. In severe cases I usually employ from three to five day intervals, and in the mild cases, or for a second and third course an interval of a week will be satisfactory. It is probable that arsphenamine is preferable to neoarsphenamine inasmuch as it is apparently a more constant product. There is no reason why a patient suffering from nervous lues should not have from forty to fifty injections in the course of the year.

The usual type of the intraspinal treatment is the Swift-Ellis. There are various modifications of technic, but the one that we employ is the same as that of Fordyce. The technic is as follows:

First, the usual intravenous injection of arsphenamine is given, employing 0.4 grams per 150 lbs. of body weight. Second, exactly thirty minutes later 50 c.c. of blood is withdrawn from the vein. This is placed on ice for three or four hours. Third the blood is centrifuged and the clear serum is pipetted off under aseptic precautions. Fourth, this serum is inactivated by incubating at 56° C. for one hour, or by being placed in a water-bath for the same time at the same temperature. The object of this is to render

inactive any bacteria that may be present in the blood stream. Fifth, a spinal puncture is done in the usual way. As soon as the stilet is withdrawn from the needle, the percolator is attached to the needle by a piece of rubber tubing about six inches in length. The percolator is held below the level of the puncture and the serum allowed to flow into this. Six c.c. is poured into a test tube so that the usual tests may be done upon it. Ten to twenty c.c. of spinal fluid will usually collect in the tube. About as much of the inactivated blood serum as there is of the spinal fluid should now be poured into the percolator and the two fluids allowed to mix. The percolator should now be raised five to six inches above the level of the needle and the fluid allowed to flow back by gravity until the original amount withdrawn is replaced. The needle is then withdrawn.

It is probable that there is no great advantage to be derived from reinforcing the blood serum before it is reinjected. By reinforcing is meant the addition of 3 to 5 mg. of neoarsphenamine, or arsphenamine, before use. Fordyce has discontinued its use, but Stokes advocates it.

Intraspinal treatments are usually given at intervals of two weeks. In mild cases of cerebrospinal syphilis three to four such treatments may accomplish the desired result, but in the severe cases from ten to twenty-five may be necessary. If there is no improvement after fifteen injections this method of attack should be given up.

The indications for intraspinal therapy have already been discussed, but one point must be emphasized; *intraspinal therapy should never be used unless the examination of the spinal fluid is positive.*

The commonest complication is pain in the legs. This is due to trauma to a posterior root. Rarely patients will not tolerate intraspinal treatment well, weight is lost, or there may be headaches or gastrointestinal disturbances.

In certain instances patients cannot tolerate intravenous injections of arsphenamine, either because of a skin reaction, or of a marked immediate or mediate reaction. In such cases it may be necessary to use the blood serum from another patient for intraspinal therapy. Naturally, this serum is withdrawn one-half hour after the administration of arsphenamine.

Despite some adverse criticism there can be no doubt but that

intraspinial treatment will yield splendid results in many cases of early tabes, in numerous cases of meningitis, or of a localized gumma, and in some cases of vascular syphilis. The results in paresis, even in the very early cases are very doubtful. The bad results which have been reported are usually due to faulty technic.

The use of spinal drainage followed by intravenous arsphenamine injections, as advocated by Dercum, has absolutely not given as good results as the method which has just been outlined.

The injection of the serum between the dura and frontal lobes of the brain, or into the ventricles is not free from danger and has given no higher percentage of successes.

The use of mercurialized serum as advocated by Byrnes is mentioned only to be condemned. I have seen at least three cases where so much irritation was produced that further puncture was impossible.

In certain cases of rapidly developing gumma a decompressive operation may be necessary in order to save eyesight.

I recall one case where a gumma of the brain developed within six weeks of the initial lesion, and which grew so rapidly that an operation on the brain was imperative in order to relieve the increased intracranial pressure.

#### PROGNOSIS

*Prognosis.*—The modern treatment of nervous syphilis gives much better results than did the old, but even yet it is a serious malady. Optic atrophy, deafness, or more or less serious paralyses may result before the condition is diagnosed, or even suspected. Incomplete treatment, which may be due to a fault upon the part of either physician or patient, is responsible for many disastrous results. As a general rule the cases of early meningitis will make a complete and apparent recovery. Most of the cases of late meningitis will do well, provided that some nerve is not injured past recovery. Probably 80 per cent of the early, and 50 per cent of the late cases of tabes can be arrested. Paresis almost invariably pursues the uneven tenor of its ways. Vascular syphilis and gummata can be benefited in a high percentage of cases. Taken all in all, the prognosis, except in paresis and early cases of tabes, is good in over 90 per cent of all instances.

## TABES

*Tabes.*—The clinicians of the sixteenth and seventeenth centuries apparently recognized early tabes. Duchenne, in the sixth decade of the nineteenth century, gave a satisfactory account of the disease as we now understand it. In 1875, Fournier insisted that it was invariably of syphilitic origin, a view which has been absolutely confirmed.

It is difficult to estimate the frequency of tabes, but certain it is that less than one per cent of all syphilitics develop the disease. It is much more common in men than in women.

The incubation period varies from three to forty-five years, with an average of fifteen.

The pathology of tabes is a sclerosis of the posterior column of the spinal cord. It is probable that this is due to a primary meningitis around the posterior roots. It should never be forgotten that there are also changes in the brain itself as is proved by the frequency of optic atrophy and certain mental changes.

The symptoms of tabes are numerous and varied, but there are eight cardinal ones. These are ataxia, loss of tendon reflexes, inability to stand or walk in the absence of light (Romberg's sign) pupillary disturbances, lightning pains, visceral crises, girdle sensation, and disturbances of the genitourinary system. Lightning pains are said to occur in 88 per cent of all cases. Loss of knee jerks in 90 per cent, girdle sensation in 31 per cent, visceral crises in 12 per cent, Argyll Robertson pupil in 80 per cent, ataxia of legs in 87 per cent, and of arms in 68 per cent, Romberg sign in 96 per cent, and bladder disturbances in 67 per cent. It is probable that these figures are derived from advanced cases as certainly early cases show only two or three cardinal symptoms.

It is difficult to say which is the first symptom of tabes. In some instances it is failing vision, in others an inability to urinate properly. Lightning pains or inability to walk in the dark are frequently the earliest symptoms.

Ataxia is usually most noticed in the gait. This is characteristic. First the patient complains that he cannot walk comfortably at night. Then he feels insecure in going up or down stairs; and soon thereafter he has some difficulty when he walks over uneven surfaces. The typical late tabetic walk is absolutely characteristic.

The feet are usually held rather far apart, the knees are over-extended and the feet are brought down with a stamp. Ataxia in the arms is noted in writing, buttoning clothes and the like. Finally complete inability to navigate may ensue.

The ataxia is due to disturbed deep sensation. It is usually found that the knee kicks and tendo Achilles reflexes are lost early and at times other reflexes such as the cremasteric or abdominal reflexes may disappear. The pain sense may be lost in irregular areas. Heat, cold, and bone sensibility may be much diminished. Some of the cranial nerves may be involved. Optic atrophy is frequent. Perforating ulcers of the foot and Charcot joints are not infrequent. At this point I should like to insist that many so-called "Charcot joints" are in reality true syphilitic joints, and that they may be much benefited by proper treatment.

It is not uncommon to find that one of the earliest signs of tabes is difficulty in walking in the dark. Many of the early cases, and nearly all of the late cases exhibit this phenomenon. The so-called Romberg test consists in having the patient stand with his arms to his side, the toes and heels together, and the eyes closed. If he sways, the test is said to be positive. This test is also frequently found in paresis.

The pupils may show inequality, extremely small in size, complete absence of reaction to light or accommodation, or the characteristic Argyll Robertson phenomenon in which there is reaction to accommodation, but not to light. At this point it may be remarked that irregularity in the shape or a slight difference in size can be made out much better through an ophthalmoscope than by the naked eye. Note should also be made of the fact that a slight flattening of the pupil, or a pupillary inequality by no means invariably indicates the presence of cerebrospinal syphilis. In my office six or seven patients showing these signs have been submitted to spinal puncture and nothing found. While speaking of the eyes attention should again be called to the fact that optic atrophy is very common.

Lightning pains are probably not so frequent as many clinicians would have us believe. It is true that a careful history will often elicit some complaint of more or less vague shooting pains, but the severe lancinating pains of tabes by no means affect every individual who suffers from the malady. These are most common in the



sciatic region and may last a few moments or even for hours. They are, of course, due to pressure upon the posterior roots or ganglia.

The well-known visceral crises are simply another form of lightning pains. The best known are the gastric. A gastric crisis begins suddenly with violent pains in the abdomen, and there may be nausea, vomiting, and great prostration. They last a few hours and disappear suddenly. A diagnosis of appendicitis or renal colic is not infrequent.

The girdle sensation consists in the feeling of constriction around the waist. Not so much stress is placed upon this sign as formerly.

Incontinence of urine is frequently found in the late stages. Cystoscopy will often reveal a trabeculated bladder even in the very early stages. There may be residual urine and cystitis. Constipation often occurs, but at times there is fecal incontinence. Sexual desire is usually lost, but rarely is increased.

The diagnosis is not difficult. Even in the early stages a combination of several of the above symptoms can invariably be found. The blood Wassermann is positive in 80 per cent of the cases and the spinal fluid examination will almost invariably show an increase in the cells and globulin. A positive Wassermann in 2 c.c. of spinal fluid and a syphilitic change in the gold chloride reaction is usual. An alcoholic polyneuritis may give some of the clinical signs of tabes, but the laboratory findings will serve to clear up the diagnosis.

Under the old treatment tabes ran a protracted course with an average duration of from 10 to 15 years. Many cases have been arrested by the intravenous or intraspinal treatment, and I know of several instances where such remission has lasted for ten years. However, one occasionally finds cases which refuse to respond to any treatment and where the clinical signs progress even though the spinal fluid may show but few changes.

The treatment falls into four parts; education and encouragement; intravenous or intraspinal therapy; nursing; and reeducation.

The patient with tabes must always be encouraged, for treatment is necessarily prolonged and there is no chance of a grand stand play in the way of a speedy recovery. Patients should be instructed to use a cane or even crutches as falls may result in

broken limbs or other severe consequences. It may be necessary to resort to catheterization, and it is well to have a genitourinary man aid in handling any bladder symptoms.

The antispecific therapy is that already outlined in the section on treatment.

The nursing treatment for tabes includes careful cleanliness and constant watching for first signs of a bed sore. Naturally, the bedridden cases require especial care.

The ataxic process can be treated and the patient taught to use his limbs again by a reeducation process. This view was first advocated by Frankel in 1902 and since that time his method has gained universal recognition. Frankel's book, "The Treatment of Tabetic Ataxia," Philadelphia, 1917, should be consulted for details.

#### PARESIS

This condition is variously known as general paresis, general paralysis of the insane, parenchymatous cerebral syphilis, dementia paralytica, and by the laity, as softening of the brain.

The etiology is invariably syphilis; it is not necessary to assume any other factors. The causal organism was demonstrated by Noguchi and Moore in 1913, and by Hough and Nichols about the same time. Wile has succeeded in inoculating rabbits with brain substance from parietic subjects. The disease is more frequent in men than in women. It is usually stated that the Arabs are almost immune to paresis, but I am not aware that this point has been proved; at all events similar statements were once made in reference to the American negro.

The pathology of the disease is not finally settled. The process is not confined to one portion of the brain, or even to the brain itself. However, we may state that the blood vessels of the parenchyma show typical syphilitic changes; that the brain cells show various types of degeneration, and the meninges, especially where they dip down into the convolutions are much affected.

The incubation period of paresis is similar to that of tabes.

The symptoms of paresis are manifold. There are nine cardinal symptoms; mental changes, convulsive seizures, speech changes, Argyll Robertson pupil, abnormal knee reflexes, Romberg sign, ataxia, and changes in sensation.

The course of paresis is arbitrarily and unfortunately divided into three stages; the preconvulsive stage; the convulsive stage; and the stage when the patient begins to soil himself. Inasmuch as the convulsive stage may occur very early in the course of the disease it is obvious that such a criterion is of no value.

In the early stages of paresis the mental symptoms may be insidious. Patients may apparently be "neurasthenic," easily fatigued, absent-minded and subject to headaches or insomnia. There may be some lack of attention. Still others may exhibit an apparent mental overactivity and engage rashly in various new enterprises. The unwise spending of money is unfortunately only too common. Carelessness in dressing and disregard of social decorum are frequently exhibited. Careful mental examination usually reveals difficulty in association, lessened capacity for learning and loss of memory for recent events. As the disease progresses the mental condition becomes marked. The well-known delusions of grandeur affect about 20 per cent of all cases. A large number of cases show depression, or a slight dementia. In the late stages mentality usually diminishes to a marked extent, although many patients maintain grandiose ideas to the end. Convulsive seizures occur in many cases.

A patient is suddenly apt to fall unconscious and to have this condition last for a number of hours, or even for a day or two. I have known these convulsions to be mistaken for uremia or diabetic coma. The disease is apt to progress following such an attack, but this is not necessarily true. As the condition goes on, speech becomes thick for certain words are slurred unless the patient concentrates upon them. Many test words are used in examination for speech defects of which some of the favorites are "Methodist Episcopal," "Third Riding Artillery Brigade," etc.

The Argyll Robertson pupil and Romberg sign have already been discussed under tabes.

Deep reflexes are apt to be exaggerated, and there may be inequality upon the two sides.

Disturbances of heat or cold sensation in the legs are common during the early stages.

The diagnosis depends upon the presence of the above clinical signs and of the laboratory findings. The latter are practically

identical with those in tabes, except that the gold sol reaction usually gives a paretic rather than a syphilitic curve.

For practical purposes the prognosis is absolutely bad. It is true that there may be long remissions but these are only temporary. Nonne has seen but four cases which recovered. It is important in dealing with the family to insist that the patient be kept from spending money lavishly, and possibly reducing himself to the condition of a pauper. In the great majority of cases the duration of the disease is from three to four years, and the limits are from three months to ten years.

Treatment is most unsatisfactory. It is true that some enthusiasts believe that they have effected wonders in certain cases, but let us remember that remissions occur in untreated cases. Inasmuch as it is possible, but not probable, that we may do good in the early stages, it is probably well to give intensive Swift-Ellis treatment for as long as the patient does not change for the worse. Once, however, it is clear that the disease is progressing, there is no sense in further treatment, except in commitment to an institution.

#### TABOPARESIS

Taboparesis is believed by some to be a high tabes, and by others to be a low paresis, and by still others to be a mental paresis and a neurologic tabes. Pathologically it seems to be something more than a paresis for the disease processes predominate in the cord. The disease usually shows a more insidious onset than paresis and runs a longer course. The characteristic symptoms are hypotonia of the legs, lightning pains, visceral crises, ataxias, and the loss of the patellar reflexes. The laboratory findings are similar to those already given. The gold sol reaction is apt to show a paretic curve, but may show a syphilitic one.

Treatment is almost as unsatisfactory as in true paresis.

#### VASCULAR SYPHILIS

The large blood vessels forming the circle of Willis are not infrequently the site of one or more small aneurysms. Combined with these lesions there may be a more or less localized meningitis and the meningitis is much more apt to produce early symptoms than are the aneurysms. Naturally, the symptoms from meningitis

would be those of either a basal meningitis or a meningitis of the convexities; both of which will shortly be discussed. The usual fate of aneurysm is rupture, and rupture of a cerebral vessel naturally results in the symptoms of apoplexy. As a result death may occur and there may be a mono- or a hemiplegia. Paraplegia is rare. Any paralysis occurring in a person under 40 years of age is usually syphilitic in origin.

The following case report will illustrate the symptoms and dangers of this type of disease:

The patient was a male, age 28 years, who was first seen with a genital chancre. He had two courses of arsphenamine, and mercurial treatment, his total course lasting eight months. Two years later general physical examination, Wassermann, provocative Wassermann and Luetin reaction were all negative. The patient would not submit to a spinal puncture. One month later he suddenly developed a paralysis of the right external rectus muscle. Spinal puncture at this time revealed a high cell count, an increased globulin reaction and a syphilitic gold sol curve. The spinal fluid Wassermann was negative with 2 c.c. of fluid. For two years the patient was given thorough intraspinal and intravenous treatment. He then disappeared from sight for six months. At the expiration of that time he suddenly died, and autopsy revealed that an aneurysm had ruptured. Under ordinary circumstances vascular syphilis of the brain is not apt to develop after such thorough treatment and the spinal fluid Wassermann is usually positive, but otherwise this case report is typical of the disease.

The prognosis in these cases is always dubious for it is well known that an aneurysm cannot be cured.

Treatment consists in the usual intravenous or intraspinal medication, for thus we may prevent the formation of any new aneurysms.

#### BASILAR MENINGITIS

This is a common condition as syphilis of the nervous system tends to show a predilection for the base of the brain. The symptoms are varied, depending upon the amount of involvement at some particular spot. Headache, sometimes worse at night, is one of the most frequent complaints; vertigo, and occasionally deafness may occur. Optic neuritis is common. The olfactory nerve is sometimes involved.

Mental symptoms are rarely prominent features. Apathy is the rule. There may be a fairly characteristic symptom complex of melancholia, mania or dementia. The usual changes are found in the spinal fluid. Treatment is that already indicated.

#### MENINGITIS OF THE CONVEXITIES

This condition is frequently associated with basilar meningitis, but this is not necessarily the case. The most common symptom is headache. At times localized tenderness can be found. Convulsions of the Jacksonian type may occur. Sensory disturbances necessarily depend upon the areas involved. Temporary aphasias are fairly common. Monoplegia is frequent. The laboratory findings are similar to those in basilar meningitis and the treatment is the same.

#### DIFFUSE CEREBROSPINAL SYPHILIS

As a matter of fact most cases of syphilis of the nervous system are diffuse, but it is convenient to describe cases of meningitis of both the brain and the cord as an entity. The disease may show within a week or two after the appearance of the initial lesion, or it may not manifest itself for many years; as many as forty years in one case which I had.

The general symptoms are headache, vertigo, insomnia, irritability, tremors, perhaps slight ataxias and occasionally a very definite paralysis due to the pinching of a nerve by the meninges. Neurologists are very apt to emphasize many mental symptoms, but these are not frequently seen by a syphilologist for the good and sufficient reason that they are apt to be the terminal rather than the early symptoms. Disturbances of the bladder and sexual power are not uncommon. Examination will usually reveal one or more of the following signs: changes in the shape or size of the pupils, pupillary inequality, abnormal pupillary reactions, possible changes in the fundus, disturbances of hearing, disturbances in some of the reflexes, tremor, ataxia, Romberg sign, or sensory disturbances.

The diagnosis must be made from multiple sclerosis, general paresis, tuberculous meningitis, and multiple malignancy of the lepto meninges. Multiple sclerosis usually shows three symptoms which are rare in cerebrospinal syphilis; scanning speech, inten-

tional tremor, and nystagmus. As a general rule multiple sclerosis shows a slight increase in the cell count or the globulin content of the spinal fluid. The Wassermann is negative. The gold sol reaction has been reported to yield either a syphilitic or a paretic curve. Tuberculous meningitis and malignancy can usually be ruled out by the examination of the cerebrospinal fluid, the Wassermann reaction and the gold sol reaction being negative. Paresis usually shows more mental changes than does diffuse cerebrospinal syphilis. Treatment is that of the recently mentioned conditions.

#### GUMMA

A solitary gumma may develop in any portion of the brain. Naturally, it is most apt to occur some years or more after infection, but I have seen one never to be forgotten case where it developed even before the appearance of the secondary eruption.

The symptoms are those of a brain tumor, namely, increase of intracranial pressure with the usual headache, optic neuritis, and vomiting. Localized symptoms depend upon the location of the growth. Spinal fluid usually shows the changes characteristic of syphilis. Operation may be demanded in order to relieve the pressure. After this is done intraspinal treatment should be tried from the start as there is no time to be lost.

#### SYPHILIS OF THE PERIPHERAL NERVES

Peripheral nerves can show involvement in a number of different ways. The most common is where they are "squeezed" by a syphilitic process in the meninges at the point where they emerge from the skull or spinal column. Naturally, gummata or enlarged lymph nodes may also cause undue pressure upon them. However, the nerve sheath itself may be infiltrated. It is still a mooted question whether or no a simple specific degenerative polyneuritis may occur.

#### NEUROSES AND PSYCHOSES

Syphilis not infrequently leads to a feeling of inferiority which may prove serious, as a marked depressive state may result. I have had two patients commit suicide as a result.

The most valuable work has been done by Plaut, who describes ten varieties of syphilitic psychoses. These are:

(1) Simple syphilitic weakness of mind is usually due to a gross lesion of the brain; there is usually a hemi- or monoplegia.

(2) Syphilitic pseudoparesis is a difficult condition to diagnose as it lies midway between cerebrospinal syphilis and paresis. There are often auditory hallucinations. These cases usually do well under treatment.

(3) The paranoid state may occur with tabes. There are delusions of persecution and frequently auditory hallucinations.

(4) A paranoid state without tabes is rare and somewhat resembles alcoholic polyneuritic conditions.

(5) Epileptic forms of syphilis are difficult to differentiate from true epilepsy, except by spinal fluid examination. Convulsions occur as a result of thrombosis of cortical vessels. They may show religiosity, hypoeirisy, preconvulsive excitement, confused periods, dream state and other evidences of true epilepsy.

(6) Short hallucinatory confused states are transient and resemble the confused periods occurring in the epileptic forms.

(7) Psychosis with syphilitic cardiac disease shows irritability, apprehension, depression and memory defects.

(8) Psychoses resembling manic depressive insanity resemble more or less closely the real disease, but the delusions are usually more grotesque. Spinal fluid examination will usually be necessary to clear up the diagnosis.

(9) Mental disorder due to syphilis as a psychic trauma may take the form of syphilophobia, or an undue fear of the consequences of the disease. Syphilophobia is a disease much better handled by the alienist than by the syphilologist.

(10) Various grades of either weak-mindedness or faulty development are apt to be due to congenital syphilis rather than to the acquired type.

Syphilis furnishes many cases for the insane asylums. This is usually estimated at about 15 per cent, but may be a trifle higher. The cases admitted to the asylums are usually paretics, tabetics and cases suffering from mono- or hemiplegia and certain conditions mentioned in the preceding paragraphs.



## SYMMETRICAL SYNOVITIS OF THE KNEE IN CONGENITAL SYPHILIS (CLUTTON'S JOINTS)

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(Received for publication, June 22, 1922.)

CLUTTON'S paper entitled "Symmetrical Synovitis of the Knee in Hereditary Syphilis," published in 1886, begins with the following statement: "The fact that the condition of which the title of this paper gives the most prominent feature has been little noticed in our surgical literature tempts me to make a few remarks as to its clinical features."

Von Hippel in 1903 in a paper on the same subject said: "A recent search of the literature makes it apparent to me that in surgical circles the opinion still prevails that joint affections are rare in hereditary syphilis."

Dunlop in 1904, said: "The subject of syphilitic synovitis in children has not received the attention it deserves from medical and surgical writers, and the importance of the condition entitles it to a much wider recognition than has hitherto been accorded to it. It is generally regarded as an affection of great rarity, and in the text books on diseases of children it is either completely ignored, or the subject is summarily disposed of, with the statement that such a condition is occasionally, but very rarely met with."

Fouquet, quoting Morestin, in 1909 said: "Syphilitic hydrarthrosis is much more frequent than is suspected, but if it is more common, it can be said that it is commonly not recognized."

In France, Germany and England at the present time there is more frequent mention of this condition in the text-books, but in America many of the books on surgery do not refer to it, and most of the text-books on Diseases of Children, in which one would certainly expect to find an adequate description, do not mention it. One text-book (Griffith) shows an illustration of one of Schamberg's cases and describes it with hyperplastic synovitis as follows: "A swelling of the knee joints is a not uncommon distinctly later symptom. It is bilateral and may be either a hydrarthrosis or a hyperplastic synovitis, and finally results in ankylosis."

The statements of other writers indicate that ankylosis is the result of this form of hydrarthrosis, only in the rarest instances.

There is ample evidence that the condition is a common one, and this fact together with the fact that "it has been little noticed in our literature," are sufficient reasons for again calling attention to it. As no new knowledge is to be added to the subject, this will be done chiefly by quotation from the earlier observers, whose descriptions have not been improved upon by later writers.

Symmetrical synovitis of the knee is frequently associated with interstitial keratitis. It is interesting that much of the early knowledge of the subject was given by ophthalmologists. One of the first notable communications was by Förster.

"An inflammation of the cornea, which Sämisch has described as interstitial keratitis, also bears a causal relationship to inflammatory joint affections. The joint affections are naturally called rheumatism by the patients, or rather by the relatives, for the patients are usually children. There are, however, in many cases characteristics which in many cases differentiate it sufficiently well from acute polyarthrititis and from chronic arthritis. As is the case with the latter condition, the large joints and especially the knees, are affected. The affected joints are not usually as painful as in other forms of rheumatism. I have seen many cases with copious effusion in the joints, in which the patients were limping around. Fever was absent in the cases which I have seen. Although relapses of the joint affection in the same or other joints are frequently observed, yet in general the process has a more transient, less persistent character than chronic articular rheumatism. The unexceptional results which the use of potassium iodide brought about are also remarkable. Under its administration the joint affection always disappears in four to six weeks."

Clutton gave a more accurate description than Förster and reported eleven cases, seven of his own, three of Nettleship's and one of Lawford's. In nine cases there was coincident active keratitis, in one there were traces of a previous attack. One showed no corneal affection. Five had notched central incisors. Four had nodes on the tibia, two had absolute deafness of recent origin. In all the presence of congenital syphilis was established beyond a doubt. Since the appearance of this paper, the condition has commonly been known as "Clutton's Joints."



Fig. 1.





Fig. 2.





Fig. 3.





Clutton reviews the cases as follows: "The average age of the patients was about fifteen. The predominant features of the disease were the symmetry of the affection, the freedom from pain, the long duration of the symptoms, and the free mobility of the joints on passive movement throughout the course of the disease. I have never seen both knee-joints fill with fluid, causing scarcely any pain or discomfort, whilst other joints remain quite free from any signs of inflammation, except in cases where there was distinct evidence, either past or present of hereditary syphilis. The patient generally complains of stiffness in one knee, which is found full of fluid, but not tense; on careful examination the other knee is also found to contain fluid, but not to the same extent as the one for which advice is sought. So that it is fair to assume that the knee to which attention has been directed by the patient has been affected some time before he has felt any inconvenience. In a few instances there has been an interval of some months before the knee has given the ordinary signs of synovitis; and in one case, which was that of a patient aged twenty, there was an interval of two years. The swelling in some of the cases was accompanied by considerable thickening of the synovial membrane; and in one instance recorded by Mr. Nettleship, the observation is made that in some places it gave the 'impression of loose bodies in the joint.' The chief part of the swelling seemed to be produced by an increased quantity of synovial fluid. The joints were never tense, but gave a sensation of flaccid fluctuation, as if they were only half full of fluid. The bones in the immediate neighborhood were not enlarged, and in only a small proportion of the cases was there any particular tenderness. The ultimate result in all the cases that came under my observation was the perfect recovery of the joints, the most important part of the treatment appearing to be the exhibition of antisyphilitic remedies—mercury and iodide of potassium; but these drugs had not the same marked effect that they have in the acquired disease. I am at a loss to explain why the knees should be affected in preference to other joints. It is probable that with further observation the knees will not be found to occupy this solitary distinction, and that other joints will be seen to be affected in a similar manner."

Von Hippel gave interesting data on 77 cases of congenital

syphilis, in 66 of which he had made careful notes on the condition of the joints.

In the series of 77 cases, 43 had joint affections. I have tabulated them.

Total cases with joint affection	43	(56%)
Knee joint	41	
Knee joint with much swelling	36	(33 bilateral)
Knee and other joints	6	(Elbow 4, wrist 2, finger 1)
Other joints (knee not affected)	2	(Elbow 1, several joints 1)
Interstitial keratitis	35	
Joint affection preceded keratitis	32	(By less than 1 year 13, by from 2 to 10 years, 10)
Keratitis and joint affection simultaneous	2	
Keratitis preceding joint affection	1	

In 39 cases with definite joint swelling the ages were as follows:

0—1 year	3
2—5 years	5
6—10 “	15
11—15 “	6
16—20 “	9
21—25 “	1

Only in exceptional cases was there much pain, and in many cases the patients had not sought medical advice for the joint affection.

The other findings agree so closely with those of Clutton that it is unnecessary to quote them. Von Hippel believes that symmetrical synovitis is a more common manifestation of congenital syphilis than Hutchinson teeth, that in cases of suspected congenital syphilis it is incumbent on the physician to look carefully for any signs of the condition. He notes that in most cases there was a tendency to spontaneous healing in the course of several months, and that mixed treatment is effective. He refers to cases in which surgical interference was resorted to, the surgeon not having thought of syphilis.

Dunlop briefly summarizes the most striking features of chronic syphilitic synovitis as follows:

“1. Its insidious development. 2. Its chronic course. 3. Its symmetrical distribution. 4. Its freedom from pain, and the mobility of the joints on passive movement. 5. Its association with other syphilitic stigmata. 6. Its amenability to treatment.”

Little has been added to these early descriptions of the disease.

As few cases need any operative interference or come to autopsy, little is known of the histopathology. At the present time x-ray findings are available. They add little or nothing to the knowledge previously acquired, but are of assistance in differentiating this from other joint affections in doubtful cases. The accompanying cuts show a typical case. The x-ray photographs show the bones unaffected, a markedly floating patella, and considerable separation of femur and tibia.

There should be little difficulty in the diagnosis of this affection, except perhaps in the rare cases in which a joint other than the knee is affected and the knee is unaffected. Syphilitic epiphysitis in most cases could be easily excluded, and in doubtful cases an x-ray photograph would settle the question. If the condition is thought of and the patient carefully examined there is no difficulty in differentiating it from tuberculosis of the joints.

Most cases improve gradually and completely recover with anti-syphilitic treatment. A firm bandage may be applied to the joint. D'Arcy Power reported a few cases in which tapping the joint was resorted to when the swelling did not respond to other treatment.

A few references to the more important papers on the subject have been appended.

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## INCIDENCE OF SYPHILIS

### AN ANALYSIS OF 1088 AUTOPSIES\*

BY WILLIAM W. HALA, M.D., BROOKLYN, N. Y.

(Received for publication, May 9, 1922)

SOME time ago, the U. S. Public Health Service sent questionnaires to the pathologists of the different hospitals of the country, regarding the percentage of deaths, in which lues might properly have been the potent factor. It is obvious that it is unquestionably difficult to make any dogmatic statement, or to render any definite decision in this matter, and yet the careful analysis of cases, occurring over a lapse of years, particularly in a large city hospital, furnishes important information regarding that protean disease known as syphilis, and brings into more or less clarity, the inordinate amount of syphilization, that is apparently endemic, in our population.

The following communication is based on an analysis of 1088 cases of death, coming to autopsy. Its object is to estimate as accurately as possible, the percentage incidence of syphilis, in which death may have been attributed to this disease. In attempting to establish the degree of this incidence, I have been guided by the following criteria; and no case has been classified as luetic, unless the diagnosis of syphilis has been confirmed by at least two of the following factors:

1. Clinical history of antecedent infection, or clinical evidence of existing lues.
2. Positive Wassermann reaction.
3. Typical gross lesions, observed at autopsy.
4. Histological evidence of lues.

Symmers<sup>1</sup> in 1916, analyzing 4880 autopsies performed at Bellevue Hospital, in the preceding 10 years, has placed the incidence of syphilis at 6.5 per cent. This at first sight seems very low, and indeed is refuted by Warthin,<sup>2</sup> in a paper along similar lines; the latter author giving a percentage incidence of between 40 to 50

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\*Read before the Brooklyn Society of Internal Medicine, March 24, 1922.

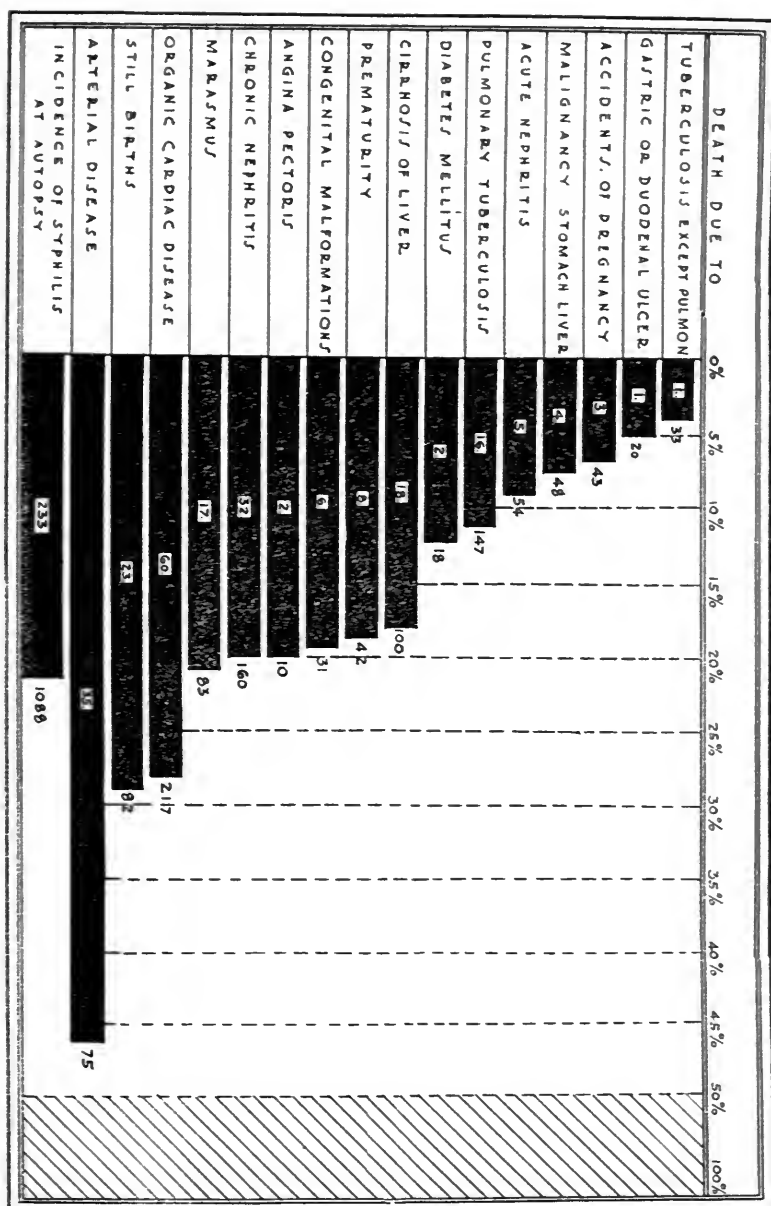


Fig. 1.

per cent, figures that are rather startling. The marked discrepancy between these two communications is explained by Warthin on the basis that the criteria employed by Symmers were mainly anatomic, while his, i.e., Warthin's diagnoses were based on microscopic data. The pathologic diagnosis of lues is indeed only accurate when confirmed by the typical histological picture, particularly when substantiated by the demonstration of the *Treponema pallidum*. In acquired syphilis, this demonstration is exceedingly difficult, as every pathologist will concede, so that in the majority of cases, the histologic diagnosis should be confirmed by serologic or clinical facts. It is not within the scope of this paper to discuss the "raison d'être" of why the treponema is so difficult to locate in the tissues, the seat of acquired syphilis, on the one hand; and so easy to demonstrate in congenital syphilis, on the other.

Because of the lack of a sufficient number of cases, the present paper does not include cases in which death was due to infectious disease, or diseases of the nervous system. I have endeavored to include the most common causes of death. In many of the cases, syphilis was the direct etiologic factor in the production of the disease, and therefore the underlying, if not the direct cause of death; in some of the diseases selected, the existence of syphilis was probably coincidental. Guided by the criteria already mentioned, the analysis of the 1088 autopsies, has shown that in 233, a definite diagnosis of luetic infection could be made; a percentage incidence of approximately 21.4 per cent. Table I is presented, in order to show, as concisely as possible the results of the analysis, while the diagram gives pictorially the incidence, the diseases being listed so as to show a gradual rise.

A careful examination of the Table and Fig. 1 will disclose some interesting facts. While this communication is intended to be mainly statistical, a brief discussion anent the reason why the cases were listed as syphilitic may not be amiss.

#### PULMONARY TUBERCULOSIS

As already stated, the existence of syphilis, in some of the diseases analyzed was only coincidental. This is particularly true in the case of the deaths due to tuberculosis. All of the 16 cases had a positive Wassermann. Carrera,<sup>3</sup> in a paper published in the *Journal of Syphilis*, has written an excellent monograph on pulmonary syphilis.

TABLE I

DEATH DUE TO	LUETIC CASES		AUTOPSIES	PER CENT
Pulmonary Tuberculosis	16	in	147	10.8
Tuberculosis (other organs)	1	"	33	3.03
Malignancy (stomach, liver)	4	"	48	8.27
Gastric or Duodenal Ulcer	1	"	20	5
Cirrhosis of Liver	18	"	100	18
Diabetes Mellitus	2	"	18	11.11
Organic Cardiac Disease	60	"	217	27.6
Angina Pectoris	2	"	10	20
Arterial Disease	35	"	75	46.6
Acute Nephritis	5	"	54	9
Chronic Nephritis	32	"	160	20
Accidents of Pregnancy	3	"	43	6.9
Diseases of Infants				
Marasmus	17	"	83	20.4
Prematurity	8	"	42	19.04
Congenital Malformations	6	"	31	19.3
Stillbirths	23	"	82	28.04
Totals	233	"	1088	21.41

The diseases listed above are among those included in the questionnaire sent out by the U. S. Public Health Service, and credit is due that Department for instigating this compilation.

He has laid particular stress on the presence of fibrosis occurring in the region of the hilus of the lung, endarteritis of the pulmonary vessels, and peribronchial thickening. Many of the cases of pulmonary tuberculosis observed, showed these lesions, which, however, could not be attributed solely to lues. Subpleural aggregations of small round cells, (miliary gummata ?), were noted in a considerable number of cases. Treponemata were not demonstrated.

#### TUBERCULOSIS OF OTHER ORGANS

One case was selected from the 33 autopsies, because it showed an advanced aortitis with beginning sacculaton of the ascending arch. This was a case of tuberculous pyelonephritis.

#### MALIGNANCY OF STOMACH, LIVER; GASTRIC AND DUODENAL ULCER

Here again the incidence of syphilis was probably accidental, and the diagnosis was made because of positive serology and histologic findings in other organs.

#### CIRRHOSIS OF LIVER

Eighteen cases were listed as luetic, 10 giving positive Wassermanns, while 8 gave distinct anatomic or histologic evidence of syphilis in other organs. Of these 18 cases, 4 were examples of the hyper-

trophic type of cirrhosis, 8 belonged to the portal cirrhosis group, and 6 were classified as *hepar lobatum*.

#### DIABETES MELLITUS

The relationship between diabetes and syphilis has been lately discussed by Rosenbloom,<sup>4</sup> who places the incidence of lues in this disease at 12 per cent, and who further states that in 6 per cent of diabetics, the etiology is definitely treponemal. In 18 cases of diabetes coming to autopsy, two were classified as syphilitic because they had positive Wassermanns, and showed histologically a typical interstitial pancreatitis.

#### ORGANIC CARDIAC DISEASE

Among these were cases of myocardial, valvular, mural endocardial, and coronary artery lesions, stated here in the order of frequency. In one case the mitral valve was solely diseased, this case showing a positive serology, and a typical luetic myocarditis. Four cases of mural aneurysm of the left ventricle were observed, two of the patients dying suddenly of hemopericardium, the result of rupture of the heart.

#### ARTERIAL DISEASE

That lues is a factor of great importance in the production of arterial disease has been admitted for some time. This group includes aneurysms, syphilitic aortitis, cerebral arteriosclerosis among which were two cases of diffuse hemorrhagic leptomeningitis. The incidence of 46.6 per cent in this group may safely be regarded as truly etiologic, inasmuch as the diagnosis of lues was made only when definite serologic, anatomic or histologic data were available.

#### NEPHRITIS

It is within reason that syphilis is just as prone to produce lesions of the kidney as any other infectious disease. Yet the literature concerning luetic nephritis is rather limited. The recent publication of Loyd Thompson<sup>5</sup> has dealt with this type of nephropathy. Among 54 cases of acute nephritis, 5 were listed as probably syphilitic for the following reasons: 3 were clinically in the active stage of lues, two dying suddenly after salvarsan administration, while one came to autopsy as a medical examiner's case. The other



two showed coincidental acute diffuse nephritis and histologic evidence of luetic aortitis. Microscopically, the kidneys in these cases disclosed small round and plasma cell infiltration of the interstitial tissue of the kidney. Among the chronic nephritides, lues was diagnosed either because of a positive Wassermann, or specific histologic changes. The majority of the kidneys were the seat of a chronic glomerulitis, together with subcapsular miliary gummata (round and plasma cell deposits). Two of the kidneys showed amyloid degeneration.

#### ACCIDENTS OF PREGNANCY

In this group, cases dying of toxemia, eclampsia, sepsis following abortion, miscarriage, or death the result of ruptured ectopic pregnancy were analyzed. Three cases were diagnosed as luetic on serologic findings. In one case treponemata were demonstrated in the placenta and umbilical cord.

#### DISEASES OF INFANTS

Perhaps the most interesting facts are gleaned in investigating the incidence of syphilis in the newborn, or in stillbirths. The anatomic and certainly the histologic diagnosis of congenital lues presents no difficulty. Frazer<sup>6</sup> has lately summarized the findings in an article appearing in the *Journal of the American Medical Association*. The ease with which the treponemata are stained in the tissues of even macerated fetuses, contrasts markedly with the difficulty of demonstrating these organisms in cases of acquired syphilis. A careful study of the table and diagram presented with this article will show at a glance how potent a factor syphilis is in causing death among the newborn.

Before concluding, a few words regarding the prevalence of syphilis among the living may not be amiss. Various articles have appeared in medical literature, from time to time, concerning the degree of syphilization in various countries. Vedder has shown that 20 per cent of the males in Germany are luetic, while Fournier estimated that in France, 15 per cent of the adult population is infected. Hazen,<sup>7</sup> from whose paper the foregoing statements are taken, declares that in this country from 10 to 20 per cent of all hospital cases show a positive Wassermann. An analysis of the serologic work done at the Kings County Hospital during the years 1920-1921 shows

that 13.8 per cent were apparently infected with lues. In this institution the Wassermann reaction is performed as a routine laboratory examination. This incidence seems to support the statement of Hazen alluded to heretofore.

In conclusion, I desire to express my thanks to my assistant, Dr. R. W. Auerbach, and to Mr. Franz Janke, serologist, for the valuable help and suggestions that they freely offered.

#### SUMMARY

The incidence of syphilis in 1088 autopsies, after careful analysis is 21.41 per cent.

Cardiovascular diseases among the adults show the highest degree of incidence.

Syphilis is an important factor in the causation of death among the newborn.

The percentage incidence of lues among patients of a large city hospital is estimated at 13.8 per cent.

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- <sup>5</sup>Loyd Thompson: Jour. Am. Med. Assn., lxxv, No. 1, pp. 17-20.
- <sup>6</sup>Frazer: Jour. Am. Med. Assn., lxxvii, No. 21, pp. 1623-1627.
- <sup>7</sup>Hazen: Jour. of Syphilis, vi, No. 1, pp. 1-54.

## FROM FRACASTORIUS TO EHRLICH

BY A. RAVOGLI, M.D., CINCINNATI, OHIO

(Received for publication, February 26, 1922)

**H**IERONIMUS FRACASTORIUS was the first to give to the *Morbus Gallicus* the name *Syphilis*. He wrote a poem which was published in the year 1521. Last year, 1921, was the Fourth Centennial Anniversary when this disease was made known amongst the people. We can congratulate ourselves upon the advancement which has been attained in the last few years from the works of Schaudin and Hoffmann, Wassermann, Ehrlich and many others. Obscurities which surrounded this disease have been cleared up concerning the cause, the diagnosis and the treatment.

Fracastorius was born in Verona in 1483, studied in Padua in the gymnasium, cultivated philosophy and mathematics, and seriously applied himself to the study of medicine. At the age of twenty when he had not yet finished his medical studies, Emperor Maximilian brought war to Italy. His studies were interrupted and after receiving the news of the death of his father, he was compelled to go back to Verona. Bartolomeus Liviani took him under his protection and sent him to Portenone where he obtained the diploma of Doctor of Medicine. Liviani was compelled to go to the field of battle and Hieronimus went with him. After the massacre of Ghiera d'Adda, Liviani was taken prisoner by the French troops, and Hieronimus returned to Verona. There he began practicing medicine and meanwhile was studying astronomy and poetry. His name as an excellent practicing physician was soon known, and so much esteem did he gain, that the Pope Paulus III asked him to accept the position of physician to the Council of Trient, which he accepted. He recognized that an epidemic was spreading, and he advised the members of the Council to leave Trient and go to Bologna for safety.

He followed the Latin poetry, and his poems were in great esteem and were compared to those of Cotto and Bembo. His name was known to Charles V, German Emperor, and to Francis I, King of France. Margaret of Valois requested him to make France his

permanent residence, which he declined. He had helped Fernelius in a very grave and sad occasion. Hieronimus died in his villa on Mount Incaffi on the 6th day of August, 1553, from an apoplectic stroke. One son, Paul, remained, two others having died previously. The funeral was held in Verona and he was buried with solemn ritual. The city, grateful to such a good citizen, ordered a marble statue, which was made by Danesius Cataneus in 1555. Poems were written in his honor and medals with his portrait were coined. Many biographers, as Rhamnusius F. Pola, wrote the biography of Fracastorius in Italy. From among the foreigners must be mentioned Frid. Otto Mencken, who wrote a complete biography, published in Leipzig under the title "*De vita, moribus, scripseis, meritisque in omne literarum genus prorsus singularibus H. Fracastorii*" and William Roscoe in the biography of Leo X. and P. A. Budik: *Leben und Wirken der vorzüglichsten lateinischen Dichter des xv. bis' xviii. Jahrhunderts.* Wien 1827, Vol. xi.

Fracastorius, besides the poem "*Syphilis sive morbus Gallicus*," wrote many other works, some in prose. The poem *Syphilis* which he dedicated to Peter Bembo is considered an excellent work in liberal arts. It was printed in Venice in 1555, in London in 1591, and in Geneva in 1637. Many editions were made in Italy, in Verona, Rome, Naples, Bologna and Cremona. It was also translated into several languages, and was comprehended in the Luisinian Collection *de Morbo Gallico*.

The poem of Fracastorius is divided into three parts. The first part points out the origin of this strange disease which had affected many regions of Europe, Asia and Africa. In Italy the disease was spread by the French troops, and for this reason it received the name from the importers.

With a magnificent poetical apostrophe he appeals to Apollo to reveal the cause of the disease and to speak to the Goddess to tell what causes had produced such an unusual pestilence. Is it not possible that the cause rests with those men (alluding to the crew of Columbus) who leaving from the Spanish shores tried to explore unknown seas and lands opposite to ours? In those lands on account of the bad condition of the sky diseases are constantly found entirely unknown to other people.

The contagium from those lands was carried to our countries and as it found the people not so strong to withstand the infection,

spread and attacked all European countries. Just like a prairie covered with ripe grasses if set on fire the dried plants burn, the fire advanced towards the forest, the sky is red illuminated by the flames. Those who carried the disease amongst us had never been sick before, they were living in the best of health; in coming back they were so sick and so infected as to be a menace to others. Spain had never known of such a disease before those men dared to plow with their vessels the unknown sea.

The reason of existence for the disease is not one but many, and for all is difficult to explain, and to get out of the obscurity. Elephantiasis had never been in the Italian countries, neither lichen nor sycosis, which afflicts the populations on the Nile. The cruel lues is of the same kind; it is not transferred by air, but it is hidden in darkness. In our countries it had never been seen and it was not even known under any nomenclature. What the air and the soil may bring spontaneously may be changed after many years. If you wish to know all the causes, look around the world, how much it was debased by the vice which infected all cities.

In the cities the seeds of the lues are found. The poet speaks of possible changes in the air and in the seasons, of new diseases and of new contagion affecting the living people. Scarcely one hundred years have passed, when in the regions where the Ganges flows an insolation fever arose, which affecting the chest caused the patients to expectorate bloody spit and with miserable face brought them to death on the fourth day. Syrian and Persian people, who drank the water of the Euphrates and of the Tigris were infected after a short time, then the Arabs and the Phrygians, until it finally reached Europe and Italy.

Fracastorius practically described the conjunction of Mars and Saturnus in the sign of the Cancer, which took place in the year 1484 and from that emanated the thought to find the origin of the French disease.

After describing a disease which affected the sheep, he points out the difference in the nature of the contagia, and the different ways by which they spread from one to another. This condition did not infect birds, or animals living in the wilderness, or oxen, sheep, and horses, but the most noble of all, the human kind, infecting his blood which is by its nature thick and slow. If you care to know the signs produced by the contagium in those affected, you may hope to

find the verses so interesting that they may remain to be read by your posterity, and the knowledge of the signs and of the face of the infected will be of advantage to them.

If it should happen that the contagium would lose its strength and die, even after centuries, the scourge may revive and attack humanity with the same symptoms.

The disease saps the power and the vital strength, the patients are oppressed by extraordinary torpor and languor and then cannot attend to their duties. The vigor of the eyes is lost and the color of the face is pale. Ulcers in the genitals are slowly spreading, eating up the inguinal regions.

Then the signs of lues are made more manifest, and when the daylight is disappearing the darkness causes sad and miserable nights. And when the patient is covered in bed to have the pleasant heat, the arms, the shoulders, the legs are affected with unbearable pains. The contagium has gone into all the veins infecting the humors and the nutrition of the body. Nature usually tries to remove the infectious elements from the interior of the body towards the external parts but on account of the tardy circulation and of the thickness of the humors and of the tenacity of the disease is not able to free the system. In consequence the bloodless limbs become swollen and cause pains in the small joints.

The disease then takes the way of the skin, and aches (pustules) spread all over the body, deforming the face.

He describes under the name of pustula the mucous patches of the scrotum and fossa crurogenitalis, from which mucous sanies and corruption were oozing. He describes the ulcerated patches of the tongue and of the mouth and the hoarseness of the voice. The patients are dragging the most miserable life, sighing with deformed eyes, and are calling gods and stars cruel to them. The image of the day and the image of the night is horrible to them.

He refers to a fine young man, rich and strong, who was the idol of the young ladies of the highest society. He had been infected with the disease, lost his eyes, his limbs full of sores, so hideous that he was shunned by everybody.

After a practical apostrophe to Jupiter and to Saturnus praying to free Italy from the scourge, he decries the struggles of the Italian political factions and the invasion of the French troops under Charles VIII who were considered the carriers of the pestilence and

referred to Verona and to Venice. He decried the King of France who had brought War to Italy, and with sword and fire had ruined Liguria, and kept the whole of Italy in mourning, despair and grief.

In the second book the poet asks: What changes in the manner of living, what remedies have to be employed to oppose a terrible scourge? At first men having no knowledge of the disease, or experience have tried many different drugs and many means to try to break the chains of the pestilence and he who would be able to find such a remedy has to be as a victor transported to the sky. Even if cruel weather and iniquitous stars have been against man, yet the presence of Divinity is not absent to concede clemency from Heaven.

In his belief the infection is much more to be feared for those who have thick blood and sluggish circulation than for those who have pure blood and good rapid circulation. From these views he advises the patient to go to the country, breathe pure air, exercise, and in this way to conquer the disease. All those infected with this disease like to be idle and to remain in bed but he does not believe should be confined to the bed for with the torpor under the fallacious image of quiet and rest the infection spreads and takes deeper roots. Keep away from Venus who is deleterious and conveys the contagium to tender and beautiful girls.

He comes to advise the kind of food to be used; the fish has to be avoided and so ducks and geese which being fat, increase the thickness of the blood. He is opposed to the use of wines.

He advises venesection to remove some of the infected blood and the use of purgatives to expel from the abdomen the humors permeated with lues.

The poet recommends many different medicinal plants, as fenil, apiumscilla, colocynthide helleborus, zingiber, myrrha, colchicum, all to be boiled together to make a decoction to be taken. He has great confidence in the therapeutic efficiency of scordion of which he recommends as an electuarius which was soon known as *Diascordia Fracastorii*.

*Styrax* and *cinnebar* is to be used to cover the parts affected with ulcers but the best use is for fumigation by means of which the horrible lues and the dire contagium is removed. The remedy however is very severe and causes affection of the mouth. For this reason it must not be used for the whole body but only for the parts where are ulcers. The greatest therapeutic efficiency is found in the

mercury argentum vivum, with which is found an admirable action which dissolves condensed humors.

“Argento melius persolvunt omnia vivo  
Pars major, mirande etenim vis insita in illo est.  
Quodque est condensum humores dissolvit.

\* \* \* \* \*

Colliquant concreto et semina pestis inurunt.”

and like a flame burns the seeds of the pest. The invention of this remedy is really a divine gift. Here comes an interesting poetical recount of how the mercury was found. To Callirhoe, a nymph, who has the power to chase away disease, the poor afflicted present violets and roses if she relieves them from their sufferings. In fact Callirhoe leads a young man into a cavern which was covered with moss, where a rivulet was running between rocks, producing a pleasant and quieting noise and there he found a river of quick silver. He saw nymphs preparing fires and boiling and treating quick silver. “I know why you come to this obscure place. I know your name and the name of the infection is known to me, also why you come here. Shake off from yourself all fear; Callirhoe sends you here in order that in the depth of the earth you may find health. Pick up your courage and follow me in the obscure paths of the cavern and I will introduce you to the divinity.” He went astonished, amazed between the abysses and the rivers where the gods had their abode. Here he found the origin of gold and of silver and was told, this is the place which mortals consider to be their goal, where the metals are formed. There he saw the Cyclopes of the Etna melting and pouring molten bronze. “The left hand road leads you to them. The right side roads brings you to the sacred river, where you will find the living metal from which you hope to obtain health. After you have been immersed three times in that river, all corruption will be taken out by the fluid metal.” After that he saw his limbs and his body pure, free from the pest which was adhering to him.

The remedy obtained confidence and fame amongst the people. The mercury begun to be mixed with lard, to which after a while turpentine was added together with several oils and sulfur. With this ointment the body was to be rubbed, and do not believe it to be obscene, because this inunction removes the disease and there is



nothing more obscene about it. Do not rub however the head and the surroundings of the heart. After rubbing the body it has to be covered with heavy blankets to promote sudation and the impure substances come out in drops. This treatment has to be repeated every five days. The liquefied excretions of the disease will be seen come out from the mouth, where small ulcerations may be formed. At this time some good wine can be used to wash the mouth and produce strength. The patient can be considered well though he needs some hot baths and some aromatic potions of rosmarin and verbene.

In the third book the poet expounds the praise to a holy tree, which he calls the great gift of God. It was found in and imported from the land recently discovered and gives relief to the pains. He prays the Goddess Urania to have the tree vegetate and spread its branches in Italy. He wants men to go to the newly discovered world and give to these people our language and laws. Happy will be that man who is capable of such an achievement. For him it is enough to refer to the efficacy and use of this tree which many come to use from so long and so far away across the sea.

In the middle of the great ocean under the burning star of Cancer where the sun shines and which in our country is hidden, there is an unknown Isle which was called Hispanam by the men who found it. That land is rich in gold but much more so in the tree, which the inhabitants call Hyacum. This tree is tall and large and has a rich top full of leaves and between them is a small acrid nut which is hard as iron, a gummy resinous humor oozes from the trunk. It is cultivated by the natives with great care because this is the only hope for a cure for lues which is perpetually found in those places. They remove the bark from the limbs and gather the humor which flows from the cuts. This is boiled, the scum is removed and the remnant is used on those suffering with ulcers. What remains is boiled again, honey is added and a quantity is given to the sick in doses sufficient for a month. This ought to be taken with certain rules: when the star Lucifer comes up in the East, when the Luna has finished its orbit, and no wind or cold air may disturb the potion.

The diet has to be prescribed and the patient must not be fed too much; he has to eat just enough that the body does not suffer from fasting. The power of the remedy is such to rebuild and to give strength.

The remedy entering into the body drives out after two hours a copious sweat, which frees the body from the pest and no pustula shows on the body. The limbs have no more pain and youth comes back as a flower. God has shown to those people the use of so powerful a remedy and fate has given such an abundance of forest. The sailing boats were plowing the waves of the unknown ocean and the Nereides were amazed to see them run with displayed sails. It was night and the moon was splendid and giving light to the bridge of the boats. The Commander of the little fleet raised a prayer to the moon to give them the chance to land in those so much longed for arbors. The moon listened to the prayer and ordered the Nereides to help them find the land, but she explained to them not to stop at the first island which is Ophyre. It was already daylight, the sun was in the east, clear and resplendent. They saw the hills appear and they saw the land. The sailors saluted the so much longed for land. They went on shore, tendered thanks to the Gods and took rest and care of their tired bodies. After the fourth day they spread sails to the winds and with the help of oars went between the numerous isles. He describes the Island of Quauhahani which they called San Salvador, then Anthyllia, Cuba and the Island of Gyane and Haythi, the land of the cannibals. It is not a correct geographic but a poetical description. Indeed no geographic description of any accuracy was ever given until the sixteenth century.

A description of a battle with the natives where cannons were used is given. The cannons acted on them as thunderbolts and they were so frightened that they asked for friendship and signed an act of federation. The natives brought gold, cereals, honey and made them presents and so they gave some little things in exchange. They gave entertainments also in their manners and many of them, adults, boys, and old were sad, sultry, dirty on their bodies, and full of crusts and seeping ulcers. They were placed in the middle and a white dressed priest washed their bodies with pure water sprinkled with a branch of Hyaci. Then a snow white ox was killed and the blood was let run in a patera while they were singing hymns to the sun. The crowd killed hogs and the viscera they threw out in the grass. The men from Europe remained amazed at the sacred rites never seen before. The leader said, that it was the disease, the lues, which ruins our bodies, that was sent from heaven by the offended Apollon to the cities for punishment and to avert the scourge the

fathers instituted these solemn rites. The origin was given as follows: Syphilus the shepherd was guarding thousands of white sheep, under that solstice when the prairies were dry and the forest did not afford any shade to the shepherd, or any breeze offered relief. Pitying the herd and angry on account of the heat he looked to the sun and angrily spoke. Syphilus found his body covered with hideous aches, passed sleepless nights, felt spasmodic in his limbs and from him the disease took the name and all the people called it Syphilis.

*“et a primo traxit cognomina morbus  
Syphilidemque ab eo labem dixere coloni.”*

No one can defy the divinity without punishment. All were asking the cause of the evil and what remedy. Oxen and cows were sacrificed, but it was established that one man ought to be sacrificed to the altar and that man was Syphilus. He was ready to be stabbed, when Juno forbid this and Apollo accepted the blood of the oxen. To this crime which ought to remain in memory, Syphilus was taken a vain victim to the altar. All those poor sufferers are waiting to be placed under the sacred tree and drink its juice which by miraculous efficacy expels the contagium of the horrible lues.

Really the poet does not maintain that lues was only among the inhabitants of America, but was also in Europe before the discovery of America as it is well expressed.

*“Talibus atque aliis tempus per multa trahebant  
Diversis papulis commixti e partibus orbis.”*

It was of great importance to note that the contagium was spreading in the frightened cities and yet no medicament was proposed. The disease affected mostly young people, but only a small number were suffering with ulcerated limbs. That the winds may carry away the contagium would be more acceptable, yet you Spaniards have received the first, the great present before it was known to the French, the Germans, to the Italians and to all Europe the Huyacus (Guayacus).

We greet this tree full of new medicinal properties which can be considered a gift of God and a hope for humanity, of which ought to grow forests, not only in the arctic regions or on the sands of

Lybia, burning from the sun, but on the beautiful lands of Latium and on the shores of the Tiber.

The knowledge of Fracastorius of Syphilis as expressed in his poem is nearly that which was known until twenty years ago. By the studies of Schaudin and Hoffmann the spirillum as a cause of the contagion is demonstrated every day. By the work of Wassermann through the deviation of the complement the blood shows the presence of syphilis and the degree of the infection. Through the work of Ehrlich arsenic has been found a sublime remedy, found not in a miraculous way, but by careful study and experimentation. Arsenic has been so combined as to produce no harm to the organic tissues but to kill and destroy the spirochetæ. Mercury so mysteriously found is still a great therapeutic agent, but it is not now the only remedy as it was in the past.

We can say that in 1521, Fracastorius named the disease syphilis, described the symptoms, proposed the remedy, mercury. In 1921 the veil covering the cause of the pestilence is raised, the diagnosis based on positive facts, the remedy found in arsenic, which is much more powerful against the spirochetæ. This is what the world owes Ehrlich.

## THE STANDARD OF CURE IN SYPHILIS\*

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(Received for publication, October 30, 1921)

THE standard of cure in syphilis must depend on the stage at which the disease is seen, the type of disease, and the manner of treatment employed. It is impossible, for example, to set the same standard in a case of advanced tabes, a case of dementia paralytica, a case of untreated tertiary syphilis, and a case in which the primary lesion is not yet healed. Since in advanced syphilitic manifestations one can hope only for a "clinical cure," for the purposes of this discussion the standard of cure will be considered from the viewpoint of primary syphilis. In this way we may follow the syphilitic throughout his life history.

### OBJECT OF TREATMENT

Prior to the introduction of arsenobenzene the object of treatment was understood much more clearly than it is at the present time. The question of absolute cure did not arise. It was realized fully that syphilis is intermittent in its manifestations and is capable of revealing itself in lesions of the gravest significance months or years after apparent cure. The object of treatment in the prearsenobenzene days, therefore, was to clear up existing manifestations, and to prevent their development in the future. Great syphilographers put their trust implicitly in mercury, and one finds such authorities as Fournier insisting that sufficient mercurial treatment afforded a preventive guarantee, relative if not absolute, against tabes and dementia paralytica. Indeed his statistics showed that 5.56 per cent of carefully-treated cases became paretics, while 94.44 per cent of insufficiently-treated cases succumbed.

The demonstration of the *Spironema pallidum* as the causative agent of Syphilis by Schaudinn and Hoffmann, its cultivation by

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\*Paper presented to the Seventeenth South African Medical Congress, Cape Town, October, 1921.

Noguchi, the application of the Bordet-Gengou phenomenon to the serum diagnosis of syphilis by Wassermann and Brück, and the synthesizing of salvarsan by Ehrlich, Bertheim, and Hata, altered our viewpoint considerably and led us to hope for something more. In the first burst of enthusiasm we thought we were now able to cure early syphilis with mathematical precision, and with the Wassermann reaction to guide us we felt secure from making gross mistakes. In other words the German Trinity—the Spirochaeta pallidum, the Wassermann reaction, and salvarsan—dominated our thoughts, our actions, and our better judgment.

The object of treatment soon become an assault on the positive Wassermann reading instead of an attempt to deal successfully with syphilis as a morbid condition. This was the direct result of the fact that arsenobenzene caused the rapid disappearance of symptoms and existing manifestations and that a negative Wassermann reading, or a series of such readings, was accepted as an adequate standard of cure. The chaos which resulted was complete, and only now are we beginning to realize our folly.

Before discussing the object of treatment as influenced by the remedies at present at our disposal, and therefore our standard of cure, let us first consider (1) the relation of palliating symptoms to the successful treatment of syphilis as a morbid condition: (2) the value of the Wassermann reaction as a control of treatment: (3) the question of whether cure is absolute or relative. Thereafter we will discuss our duty to the syphilitic and the best method of using the treatment measures at our disposal for his ultimate well-being.

#### THE RELATION OF PALLIATING SYMPTOMS TO THE SUCCESSFUL TREATMENT OF SYPHILIS AS A MORBID CONDITION

We will discuss this question in the light of our knowledge acquired as a result of the introduction of arsenobenzene. Since the universal adoption of arsenobenzene as a therapeutic agent of premier importance, we fear that much of the treatment of syphilis has been purely symptomatic, and the management of the future of the syphilitic merely speculative. This has resulted from the belief that, in early syphilis, a disappearance of symptoms indicated a cure, and that a series of negative Wassermann readings justified this opinion. In the light of past experience we can state definitely

that the administration of a few doses of arsenobenzene followed by a negative Wassermann reading is totally inadequate as a serious effort to treat early syphilis. Ehrlich's *therapia sterilizans magna* has not been realized. Indeed it is doubtful if the maximum utility of the arsenobenzene groups lies in the massive doses which have been advocated so long. If the spirochemicidal action of these groups were the sole factor this doubt could not be entertained. Their action on the tissues as a stimulus to active defensive mobilization is, however, a factor of such importance that it must not be lost sight of. Experimental evidence in animals materially strengthens this view.<sup>1</sup>

Undoubtedly there have been cases where definite cure followed one single course of arsenobenzene,<sup>2</sup> but such are the exception. There is also some evidence that spontaneous cure occurs in certain cases where the patient's natural resistance by the superlative production of immune bodies is strong enough to overcome the assault of the spirochete. Since it is impossible to ascertain when this is likely to occur its existence must be ignored entirely in practice.

Many attempts have been made to abort syphilis by immediate excision of destructive cauterization of the chancre, by removal of an abrasion before the chancre had appeared, and by supplementary removal of lymphatic glands which would naturally be liable to later involvement. Since generalization of the infection has occurred before the chancre appears, all these attempts have failed. The experimental work of Brandes, Neisser, and of Metchnikoff and Roux, has proved conclusively that the localization of the spirochete does not exceed twenty-four hours.

#### THE VALUE OF THE WASSERMANN REACTION AS A CONTROL OF TREATMENT

At the present time the tendency is to trust almost entirely to the Wassermann readings as a control of treatment and a guide to a standard of cure. The general standard of cure is stated in terms of negative Wassermann readings over varying periods after cessation of active treatment. How far such a proceeding is justified will appear from the following discussion.

A typical present-day standard of cure may be represented by the following: "Before giving a definite opinion as to whether a case is cured it is essential to get a negative Wassermann reaction for at

least a year in both the blood and cerebrospinal fluid, and this should continue negative after a provocative injection of '606' or '914.' For the provocative test 0.3 gm. of '606' is given, and the blood and cerebrospinal fluid are tested a week afterwards."<sup>3</sup> Such tests are liable to variation. For example at the Mayo Clinic the provocative procedure is more elaborate, seven Wassermann tests being made at twenty-four hour intervals following a single injection of arsphenamine.<sup>4</sup> The principle is the same in all, however, and it appears, therefore, that the guide to cure, and the diagnostic agent for elucidating activity, is the Wassermann reaction, even if, as O'Leary<sup>4</sup> emphasizes, the provocative procedure is not a substitute for clinical judgment but merely an accessory. In other words we are told to keep on treating patients until the Wassermann reading remains permanently negative. This apparently we have the right to expect, except in late affections of the nervous system and brain.<sup>5</sup>

To justify such a position for any biologic test we must satisfy ourselves that the test is an absolutely specific one. This, in the case of the Wassermann reaction, we cannot do. Since the antigen need not be an extract of syphilitic material or a spirochetal emulsion, and since a positive reaction may be obtained in conditions other than those of syphilitic origin, the test cannot be considered specific. Moreover its rationale is still a matter of much speculation, and its accurate interpretation a matter of opinion.

It cannot be gainsaid that the Wassermann reaction carefully carried out in the full knowledge of its many sources of error gives valuable diagnostic information regarding syphilis, in spite of the fact that the mechanism and rationale of the test are but imperfectly understood. That the reaction is only an empirical test cannot be too strongly emphasized. There is a fundamental difference between the Bordet-Gengou phenomenon and the Wassermann reaction. In the former, complement is deviated by a true antigen and homologous antibodies, which form a true complex. In the latter, however, the "antigen" is a suspension of certain lipoids, and therefore a "pseudoantigen." The complex is therefore a "pseudo-complex." In view of the fact that this test evolved from the application of the Bordet-Gengou phenomenon to the serum diagnosis of syphilis, "it is a coincidence that the reaction ever came to



be elaborated, and a very remarkable coincidence indeed that the information which it gives is accurate.'"<sup>6</sup>

Frankly we are unaware of the origin and nature of the property of syphilitic serum which forms this pseudocomplex. The evidence that it is due to true antibodies is incomplete. Nor is there sufficient evidence that this property is spirochetal in origin, either directly or indirectly. The elaboration of heterogenetic antibodies which are capable of forming a pseudocomplex with a suspension of lipoids, and therefore capable of deviating complement, is probably a large part of the explanation. Thus we find ourselves dealing with a test which is essentially empirical. Its interpretation, therefore, must have a clinical basis. We find that leprosy, certain protozoal infections, cases of hyperthyroidism,<sup>7</sup> acute rheumatic fever,<sup>8</sup> and more controversially, chronic malaria, are capable of giving definitely positive Wassermann readings. Tuberculosis also has the faculty of elaborating sufficient heterogenetic antibodies to partially deviate complement in the presence of a Wassermann "antigen." The clinical basis of the test, therefore, cannot be overstated. In this connection Tulloch writes: "I would draw attention to the fact that the only information upon which the efficiency of the test can be assessed, is obtained by sound clinical observation \* \* \* The treatment of syphilis is a serious responsibility to assume, and if the attitude of the laboratory worker be 'that it is his duty to protect the nonsyphilitic from unnecessary treatment, rather than to diagnose every case of the disease, active and latent,' he is on safe ground \* \* \* Syphilis is so protean in its manifestations that only those who have a knowledge of the multitude of ways in which it may affect the health of the individual who has acquired it, and, more important still, may affect the health of his or her offspring, can supply the information required for assessing the value of the test, and, to attain the necessary clinical exactitude involves experience which relatively few men are in a position to obtain.'"<sup>6</sup>

The place of the Wassermann reaction in the diagnosis of syphilis is well-defined. In the diagnosis of obscure conditions of ill-defined etiology the test is also a valuable aid. Its place, however, in its relation to the treatment of syphilis is not so clearly understood. The belief that a positive reading indicated spirochetal activity and a negative one meant complete spirochetal extermination has been

rudely shaken. We have encountered so often cases which we considered adequately treated suddenly developing symptoms while the serum reaction was negative, and so-called "Wassermann-fast" cases which remained symptomless while the reaction was positive, but developed symptoms as soon as the reaction became negative, that we have been called upon sharply to review the position. Realizing that we are ignorant of the origin of "Wassermann body," its relation to the living spirochetes, its duration or rate of production after complete spirochetal eradication, or the significance of its absence in the presence of symptoms, we are forced to the conclusion that the test is without value as a control of treatment.

Many indictments of the Wassermann reaction have been made particularly by Lisser,<sup>9</sup> Palmer,<sup>10</sup> Graves,<sup>11</sup> Reynolds,<sup>12</sup> Sargent,<sup>13</sup> and Oettinger.<sup>14</sup> These discussions have as their object mainly the placing of a reasonable instead of a dogmatic interpretation on the value of the reaction. The danger of treating the positive Wassermann reading instead of the syphilitic patient has been pointed out by Graves,<sup>11</sup> and by Duncan and the writer.<sup>15, 16</sup> The susceptibility of the Wassermann reaction to alcohol,<sup>17</sup> and to ether and chloroform narcosis must not be forgotten as an indication of the waywardness of the phenomenon. The test, therefore, is neither infallible nor specific, and its value is greatest when its fallacies and limitations are appreciated fully.

In spite of exhaustive modern treatment we find that active symptoms are liable to occur and recur at any time throughout the latent period of the disease, that the Wassermann reaction may vary from negative to positive and again to negative at intervals without warning or apparent reason, and that certain patients whom we are unable to classify or identify, possess an inherent potentiality to become tabetics or paretics.

Thus two distinct schools of opinion exist. One holds that the Wassermann reaction is a useful adjunct in controlling progress and treatment as expounded by Sargent<sup>13</sup> and by Rohdenburg, Garbat, Spiegel, and Mänheims,<sup>18</sup> and others. The limitations of the test are recognized, a negative reading is interpreted with caution and reservation, and the importance of many subsequent examinations is appreciated. This is a much more rational hypothesis than that entertained by extremists who simply lay down a certain

number of negative readings over a certain period as a standard of cure.

The second school is prepared to admit the undoubted value of the test as an aid to diagnosis, but is persuaded that it is without value as a means of controlling treatment. Its policy is summed up in the statement that "treatment directed against the Wassermann and regulated by it is misapplied." A positive reading in itself is not a harmful condition, being a normal reaction of the body to the spirochete.<sup>10</sup> With this opinion we concur. By treating the individual patient instead of treating his Wassermann reaction, we can do much more for him than merely turning his positive Wassermann reading into a negative one.

#### IS CURE RELATIVE OR ABSOLUTE?

This brings us to the question of whether syphilis can be cured or not, and whether cure is relative or absolute. Jacobi<sup>19</sup> states that in the light of our present knowledge the question cannot be answered definitely. In making this assertion he reminds us that reinfection is no evidence of curability.<sup>20</sup> This is a reasonable contention, for do we not meet with cases of inherited syphilis which have acquired a reinfection—the "binary syphilis" of Tar-nowsky? Reinfection in acquired syphilis also occurs, and Morrow states that in some cases the surface manifestations of a former attack were plainly evident and coincident with the eruptive phenomena of the second infection.<sup>21</sup>

At present we have no absolute proof of cure, either clinical, biologic, or serologic. Cure, then, as far as we are aware, must be relative. If we cannot with certainty cure the syphilitic, we must aim at rendering his disease sufficiently latent that the possibility of later sequelae supervening is a small one. To do this treatment must be prolonged and adequate—not merely gauged by the behavior of an empirical Wassermann reading in his serum and cerebrospinal fluid. Treatment must aim at stimulating the body tissues to an effective and protracted defensive mobilization.

Unfortunately the treatment of syphilis cannot be reduced to terms of a mathematical formula—so many doses of arsenobenzene, so many months of mercury, and so many negative Wassermann readings. The teaching of Prince A. Morrow is as sound today as when he wrote that "there is no class of diseases which so well

illustrates the principle that uniformity of practice is not a good practice. Many conditions relating to the constitution of the individual, his inherited or acquired predispositions, and his habits of life, must be taken into consideration. The indications are to treat the patient as well as the disease."<sup>21</sup>

In this connection a recent pronouncement of E. Farquhar Buzard<sup>22</sup> sums up the position very well. He writes: "We are all asked 'How long must I go on with treatment before I am cured?' For many years my answer has invariably been 'For the rest of your life.' I am never consulted about a primary chancre, but if I were my advice would be the same." Speaking of present-day treatment he says<sup>23</sup> "If you take a hundred cases of syphilis and treat them all according to the standard methods of the day you are justified in believing that a certain proportion will have been cured, but you cannot honestly tell any single one of these patients that his disease has been eradicated \* \* \* Personally I am optimistic enough to believe that if this truthful line were adopted and the patients urged to have periodic courses of treatment for the rest of their lives we should see very much less of the late syphilitic diseases than we do. As it is, a large amount of our time is taken up with the treatment of syphilitic affections of patients who have been told years ago that they had been cured of their disease, and this must go on as long as we lack the means of determining whether a cure of the disease has been effected."

#### HOW TO EMPLOY AVAILABLE REMEDIES TO THE BEST ADVANTAGE

Since absolute cure cannot be guaranteed, we must aim at the highest possible standard of relative cure. The object of treatment, therefore, may be described as being an endeavor to render the disease sufficiently latent so that the risks of later sequelae may be reduced to an absolute minimum. We must aim, therefore, at stimulating the body tissues to a prolonged defensive effort.

To this end we would advocate the employment of arsenobenzene remedies in much the same way as Fournier, Hutchinson, and Morrow, used mercury. Possibly the most satisfactory method is the subcutaneous or intramuscular administration of sulfarsenol over a long period, accompanied by mercurial medication and intramine.<sup>15, 16</sup> The parasitocidal action of the first two drugs cannot be relied on alone, and their stimulating action on the body defen-

sive mechanism must be brought into play. It has been pointed out by Schulz that large doses of mercury diminish the production of antibodies, and the same doubtless applies to arsenobenzene in large doses. Clinically we have much evidence of this, especially in the latent stage of the disease. The doses of sulfarsenol and of mercury therefore should be small, frequent, and continuous.

The method of Sicard<sup>24</sup> is admirable in that it provides for slow and steady sterilization. Small daily doses of arsenobenzene are given either intravenously or subcutaneously, 30.0 gms. being administered in a year in three three-monthly courses. This is continued for two years. Mercurial medication is employed in addition. A monthly dose of 2.5 c.c. intramine might be added to this scheme with advantage.

Experience has shown that in most cases two years of such treatment is sufficient to render the disease latent. This, however, cannot be said of spasmodic treatment with massive doses of arsenobenzene. Early cases which show active lesions and relapses at the end of this time are examples of the penalty we pay for relying solely on the parasitocidal action of the drug. As a rule more harm is likely to accrue from undertreating than from overtreating cases of syphilis.

#### OUR DUTY TO THE SYPHILITIC PATIENT

There can be no doubt that our duty to the syphilitic patient includes all the following responsibilities:

- (1) The removal of immediate manifestations.
- (2) The safeguarding against relapses.
- (3) The protection of his cerebrospinal axis.
- (4) His fitness for marriage.
- (5) The protection of his wife.
- (6) The protection of his offspring.

(1) *The Removal of Immediate Manifestations.*—This is usually a matter of no very great difficulty. Large intravenous doses of arsenobenzene are to be deprecated, however, and reliance placed on less sudden and more complete sterilization. It must never be forgotten that the generalization of the *Spironema pallidum* dates from within twenty-four hours of its inoculation.

(2) *The Safeguarding Against Relapses.*—It has been proved by

clinical experience that a short course of intensive treatment followed by a negative Wassermann reading is no guarantee whatever against early relapse. Treatment must be continued very much further, and it should be uninterrupted. Continuous treatment with small doses of arsenobenzene, mercury, and intramine, carried out over a period of two years, offers a much more reliable guarantee against subsequent relapse than a series of intensive courses consisting of massive intravenous doses of arsenobenzene and more or less continuous mercury. In the latter case the massive doses of arsenic, producing as they do an inhibition of antibody production, neutralize much of the benefit which otherwise would be derived from the continuous mercury. In the former case the antibody-stimulating-action of mercury is augmented by a similar action on the part of the *small* doses of arsenobenzene.

Having made this general statement, one must make some reference to the patient as an individual. In every case the type of treatment must be modified and adapted to the type of the disease as it affects the individual. Many factors influence the prognosis. For example, McDonagh<sup>25</sup> believes that the outlook is gloomier when the sore is papulo-indurative-erosive in type than when the sore is papulo-nonindurative-ulcerative in type: and that the prognosis is better in those cases in which the lymphatic glands are markedly enlarged and involved—that is to say in the absence of any secondary infection. So also it has been asserted that a papular syphiloderm requires a more doubtful prognostication than a macular eruption. In Feldman's series, however, this was not borne out.<sup>26</sup> It seems more probable that a severe secondary stage, procuring as it does a vigorous defensive mobilization, deserves a better prognosis than where the secondary stage is mild and the defensive apparatus is only slightly taxed. In other words, the fewer spirochetes the less antibody, or, as Harrison has suggested, the more parasites we kill the better time may it be for the rest.

Fournier<sup>27</sup> has laid down three conditions necessary to the "cure" of syphilis. These are good health, good hygiene, and good treatment. Each individual should be studied as such, and his general make-up, his inherent pathologic predispositions, his family history, and his life and habits, should receive consideration.

(3) *The Protection of His Cerebrospinal Axis.*—In 1914, Wile and Stokes<sup>28</sup> wrote: "The fate of every syphilitic with regard to the inci-

dence of cerebrospinal lues, whether this occurs early or late in the course of the disease, is in all probability determined in the first months of the infection. The infection of nerve tissue by the *Spiro-nema pallidum* is without doubt dependent upon several factors. Individual susceptibility, neuropathic heredity, alcoholism and trauma are all to be reckoned with. Moreover, the strain of the organism, hypothetically at least, may also be a determining factor in the localization of the disease process to the nervous system. That certain individuals, infected from the same source, are prone to such involvement of the nervous system, is a clinical fact well recognized. Our ignorance of the life history of the spiro-nema does not permit us to speak definitely as yet concerning the various strains. That there exist, however, in the same strain and in the same culture organisms of different degrees of virulence, different resistance and vastly different viability, is an observation familiar to all who have worked with the *Spiro-nema pallidum* in the living state. It appears to us that the explanation of the selective action of this organism upon certain systems will in time be discovered through the unravelling of its life-history and its separation into definite strains. Occasional involvement of the nervous system in the first months of syphilitic infection has been known clinically as long as the disease has been carefully studied. The isolated palsies, symptoms referable to basal meningitis and hemiplegia, have been noted quite early in the disease, and have been interpreted as evidence of precocity rather than as part of the secondary syndrome. It was not until a study of the spinal fluid early in the course of the disease was undertaken that special attention was called to a true early involvement of the nervous system in syphilis."

We have indicated elsewhere<sup>15, 16</sup> that the protection of the cerebrospinal axis is a question of antibody supply, the greater part of which comes from the blood stream. How massive doses of arsenobenzenes inhibit this supply has already been referred to. By such efforts at slow and steady sterilization as have been described already, we go a long way to safeguard the patient from later involvement of his cerebrospinal axis. For its further protection, the optic nerves should be watched closely throughout the remainder of the lifetime of every syphilitic.<sup>20</sup> For the protection of the syphilitic himself, his wife, and his offspring, a periodic systemic examination should be undertaken over the same period.<sup>11</sup> The

necessity of such examination should be impressed on each patient at the time of his discharge from active treatment, in such a manner as to make him realize its significance, and at the same time eliminate the possibility of syphilophobia developing later on. The frequency of such examinations should be dictated by the gravity of the initial process, the resistance of the patient, his reaction to treatment, and his mode of life and habits.<sup>30</sup>

(4) *His Fitness for Marriage*.—The contagiousness and susceptibility of hereditary transmission give to syphilis an unusual importance in relation to marriage. Tarnowsky has said that syphilis has an incomparably more fatal influence upon the species and on society than on the individual. Moreover no other disease is transmitted in full virulence to the offspring, and for this reason Morrow is justified when he says that "From the viewpoint of race perpetuation syphilis is antagonistic to all that the family represents in our social system."<sup>21</sup>

When, then, may a syphilitic marry? In prearsenobenzene days it was the custom to lay down certain periods of probation. Fournier<sup>31</sup> insisted on a lapse of four or five years after treatment. Hutchinson<sup>32</sup> believed that a man might marry with safety if he had continued with mercury for two years from the date of the primary lesion. Morrow<sup>21</sup> believed that Hutchinson's estimate was "medically a mistake and socially a danger," pointing out that the contagious activity of syphilis and its hereditary transmissibility were not manifest after the fourth year. He therefore agreed with Fournier, but admitted that this was not a formula based upon mathematical certainty but rather upon a calculation of probabilities. More recently in the days of arsenobenzene similar periods have been laid down by Sainz de Aja,<sup>33</sup> Bory,<sup>34</sup> McDonagh,<sup>35</sup> and many others.

If arsenobenzene and mercury are employed to the fullest advantage it seems that the laying down of such intervals is unnecessary. There seems good reason to believe that arsenobenzene may accomplish the extinguishing of the contagious and transmissive power of syphilis which previously was accomplished by time and mercury. If aluet has been treated adequately from the early stages of his infection over a period of two or three years, there is no good reason why he should not marry straight away. A positive Wassermann reading is not a contraindication. While Hutchinson



and Fournier trusted to the power of mercury to stimulate defensive apparatus and not to its undoubted parasitocidal action, so also should we, in a more marked degree, consider a similar action of arsenobenzene in *small* doses, instead of depending solely on its more immediate action on the parasite and on the Wassermann reaction.

When advising a particular individual with regard to marriage, if the patient is a man of intelligence, it is a good plan to place the whole argument of his future before him, and let him choose for himself. If he is unintelligent, neurotic, and introspective, one must assume the responsibility of advising him. Special circumstances may influence one's decision in particular cases. Such individual factors as arterial degeneration, involvement of the cerebrospinal axis, cardiovascular changes, however minute, renal implication, and so on, which are likely to shorten life or render the patient at some time in the future a bedridden invalid, must weigh in each particular case. The giving of advice in such cases is exceedingly difficult, and such contingencies as whether a few years of conjugal happiness will compensate for later years of tedious incapacity must be considered very carefully.

The responsibilities of the physician who is called upon to advise a syphilitic with regard to marriage are clearly stated by Morrow when he writes: "In the case of diphtheria, smallpox, or any infectious disease, the physician may discharge his duty by notifying the health authorities, who take proper precautions to protect others from the spread of the disease. In the case of syphilis, where there is a question of its introduction into marriage, the physician's protective duty embraces not only the prospective wife, but the children she may bring into the world, and through them the interests of society. Unfortunately, syphilis is without the pale of prevention or even recognition by the official authorities, and the physician stands as the only protector of the interests of the whole family. The question is whether his sociosanitary duty to preserve others from infection falls below his duty to protect his patient in infecting them. The answer to this question trenches upon the domain of professional ethics. In the solution of this problem, where the physician is confronted with a divided duty, common sense, as well as humanity and conscience should be invoked."<sup>21</sup>

(5) *The Protection of His Wife*.—We believe that if the treatment

which we have advocated is carried out, the risk of the man subsequently infecting his wife is very small indeed. That such a risk cannot be eliminated absolutely, however, is undoubted. Authentic observations have shown that the late lesions of syphilis may be sources of contagion. Our object, then, is to present our patient to his wife noninfective, *and to keep him symptomless throughout his married life.*

Should a married man contract syphilis our first duty is to prevent his wife becoming contaminated, and our second to prevent his wife becoming pregnant. The interdiction of pregnancy should be absolute, until such time as the conditions laid down for the unmarried man have been complied with. Should pregnancy take place, however, energetic and continuous treatment of the wife should be instituted.

That an otherwise noninfective husband may be a danger to his wife by means of conceptional syphilis should not be forgotten. The antenatal treatment of each child is therefore exceedingly important.

Should a pregnant woman become infected, what are the possibilities of the child escaping? It seems that if the woman contracts syphilis before the fifth month of gestation, the child always is infected. If infection takes place between the fifth and seventh months, a syphilitic child is born in about half the cases. Should the mother become infected during the eighth and ninth months, the child invariably escapes.

(6) *The Protection of His Offspring.*—Our duty to the syphilitic is not yet complete. It is our duty to protect his offspring, and for this we are responsible. To this end we must insist on subjecting his pregnant wife to intensive treatment throughout the whole period of her gestation. Such a procedure is advocated by Sicard, Bory, Findlay, Jewesbury,<sup>36</sup> Adams,<sup>37</sup> and many others, although, in the absence of signs, clinical or cytologic, it is condemned by Carle.<sup>38</sup> Treatment should be carried out on the lines already indicated during each succeeding pregnancy, and irrespective of the amount or nature of previous treatment. Intramine is an important factor in these cases, for the possibility of arsenical poisoning must be eliminated.

When the child is born, treatment will depend on whether symp-

toms are present or not. The Wassermann reaction is not a reliable guide in inherited syphilis. A positive reading may indicate spirochetal activity, or it may indicate the presence of a reagin derived from the mother. A negative reading, which is the rule, does not exclude syphilitic infection in the newborn. This is the writer's experience and is corroborated by that of Rolleston, McDonagh, and many others. Adams,<sup>37</sup> in a series of 37 cases of hereditary syphilis, found 36 Wassermann-negative at birth.

Should the child be apparently healthy, mercurial medication, preferably by inunction, or by grey powder internally, or by a combination of these two, should be carried out for three years. If symptoms are present, arsenobenzene is called for. In doses of 0.01 to 0.015 gm. per kilo of body weight it should be injected into the scalp veins (Findlay),<sup>39</sup> or intramuscularly into the buttock (Adams,<sup>40</sup> Jewesbury,<sup>36</sup> Addison<sup>41</sup>). Injections into the external jugular veins or into the superior longitudinal sinus *via* the anterior fontanelle are to be deprecated. Along with mercurial medication, this should be continued for three years.

#### WHEN MAY A SYPHILITIC WOMAN MARRY?

If a woman has had syphilis before marriage, and has had adequate treatment, she runs no risk whatever of infecting her husband. In spite of this fact it has been held that a woman should not marry so soon as a man who is similarly infected and similarly treated. Indeed it has been taught that her period of probation should be much longer, chiefly on account of her greater influence on the children whom she may bear subsequently. This was the teaching of Hutchinson, and a similar opinion is held at the present time by such syphilographers as Gougerot, Marshall, and others.

It is the fact, however, that, as far as our present knowledge goes, a woman who has had syphilis, no matter how drastic or complete her treatment, is *always* liable to give birth to a syphilitic child. It is therefore of vital importance in giving advice as regards marriage, to impress on her how essential it is for her to undergo intensive treatment throughout the whole duration of every pregnancy.<sup>42</sup> If this advice is given and likely to be carried out, an adequately-treated syphilitic woman may marry at once.

## TRANSMISSION OF SYPHILIS TO THE THIRD GENERATION

While transmission of certain syphilitic dystrophies to the third generation was well recognized in prearsenobenzene days, it is doubtful if such transmission still exists under the arsenobenzene régime. Sidler-Huguenin<sup>43</sup> as a result of an exhaustive study, concludes that hereditary syphilis is not as a rule, and perhaps never, transmitted from husband to wife or vice versa, or from parent to child. There is much evidence to show, however, that their fertility is very much impaired, and the number of their offspring considerably reduced. Moreover such offspring are of inferior quality, and show poor development and a great susceptibility to other diseases.

We are entitled to hope that, as a result of the prosecution of our present methods of antenatal treatment, hereditary syphilis will eventually become a rarity, and that our fears with regard to a possible increased incidence of *syphilis hereditaria tarda* will not be realized.

## A TABULATED STANDARD OF CURE

An adequate standard of cure must consider the following points:

(1) A few spasmodic massive doses of arsenobenzene cannot be regarded as a serious effort to treat early syphilis.

(2) Wassermann readings, when their fallacies and limitations are fully appreciated, are of value in diagnosis. As a control of treatment or a guide to cure they are unreliable.

(3) Treatment directed against and controlled by the Wassermann reaction is misapplied.

(4) A slow and progressive sterilization should be preferred to a sterilization which is quick and sudden and therefore probably incomplete. The drugs at our disposal should be employed in such a manner that their faculty of stimulating tissue defensive activity be utilized in addition to their parasitocidal action. Such treatment should be continued for two or three years irrespective of Wassermann readings.

(5) Each case should be treated as an individual. The patient rather than his positive Wassermann reading should receive treatment.

(6) Each case should be subjected to periodic clinical overhaul for the rest of his life. The necessity of this procedure should be impressed upon the patient at the time of his discharge from treatment.

(7) An adequately-treated syphilitic may be permitted to marry at once.

(8) The wife of a syphilitic should be subjected to intensive treatment throughout the whole period of each succeeding pregnancy. The child should be treated from birth over a period of three years whether signs of the disease are present or not. The Wassermann reading in the newborn is not a reliable guide.

(9) A syphilitic woman may marry immediately adequate treatment is complete. She also must be subjected to treatment during each gestation, and her children treated from birth.

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## STUDIES IN THE STANDARDIZATION OF THE WASSERMANN REACTION, XXIX\*

### METHODS FOR ESTABLISHING A UNIFORM AND STANDARDIZED UNIT OF ANTIGEN

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(Received for publication, March 12, 1921.)

AS shown in the preceding paper of this series<sup>1</sup> it should not be a difficult matter to decide upon the best *amount* of extract to use as antigen in the complement-fixation test for syphilis; this may be determined by a series of titrations for hemolytic, anti-complementary and antigenic activity. Insofar as standardization of the complement-fixation test for syphilis is concerned, the *kind of antigen is more important* because no system of titration can adjust for differences in essential properties of different kinds of tissue extracts.

### THE PROBABLE VALUE OF STANDARDIZING THE UNIT OF ANTIGEN AND PURPOSE OF THIS INVESTIGATION

If an agreement could be reached upon the *kind* of antigen to use in the complement-fixation test for syphilis and upon a uniform technic for titration, a great advance would be made toward standardization of technic because with these two essential matters settled, my experience has demonstrated that serologists working in different laboratories obtain remarkably uniform results by making and titrating their own antigen according to a certain technic described in a preceding paper of this series.<sup>2</sup> I repeat that if the kind of antigen, method of titration and dose to use could be agreed upon that the essentials of a standardized technic would be fulfilled and that serologists working in different laboratories, making and titrating their own antigen after an accepted technic, would observe remarkably uniform results in complement-fixation tests.

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\*From the Dermatological Research Laboratories of Philadelphia. Investigation aided by funds accruing from the preparation of arsphenamine.

A greater refinement in technic and results would be observed if a central laboratory titrated the antigen in addition to the titrations made by individual serologists, just as the Hygienic Laboratory titrates diphtheria and tetanus antitoxins and furnishes established units of toxin or antitoxin to the manufacturers.

It was with this idea in mind that I have experimented during the past six years for the purpose of developing good methods for establishing a standardized unit of antigen should serologists ever reach an agreement upon the kind and amount of antigen to employ and a uniform complement-fixation technic; the results of these studies are briefly summarized in this paper.

#### KIND OF ANTIGEN IN RELATION TO STANDARDIZING THE UNIT

A question of primary importance arises as follows: If the technic for titrating antigen and conducting complement-fixation tests could be agreed upon, would different kinds of antigen yield approximately the same or different results? For example, if the antigenic units of two widely different extracts as a plain and a cholesterolized alcoholic extract of heart were determined and ten units of each used in complement-fixation tests with the same sera, would the reactions be the same?

My answers to these questions based upon numerous experiments are as follows: In a qualitative test, that is, using one dose of serum as 0.1 c.c., with a primary incubation of 15 to 18 hours at 6 to 8° C., the results have been quite uniform insofar as positive or negative reactions were concerned. With warm incubation of one hour at 38° C. considerable differences have occurred, the cholesterolized extracts yielding more positive reactions. As previously discussed<sup>3</sup> refrigerator primary incubation greatly reduces the differences observed in complement-fixation tests employing plain and cholesterolized extracts with the same sera.

In a quantitative test employing graded amounts of serum,<sup>2</sup> differences in the reactions were observed according to the antigen employed, even with a primary incubation in the refrigerator; these differences were considerably more marked with warm incubation for one hour. Extracts containing 0.1 to 0.2 per cent cholesterol yielded stronger reactions with the smaller doses of serum although with the 0.1 and 0.02 c.c. amounts of serum the reactions with plain and cholesterolized extracts were more nearly uniform.



According to the results of my experiments different kinds of antigen titrated at the same time, in the same manner, used in the same uniform dose of ten antigenic units and tested with syphilitic sera in the same technic including refrigerator primary incubation, yield qualitative reactions of remarkably similar degree but show differences in quantitative tests employing graded amounts of patient's serum or graded amounts of complement with a constant dose of serum; the difference depends mostly upon whether cholesterol has been added to the extracts, cholesterolized extracts being more delicate in quantitative reactions than plain extracts or extracts of acetone insoluble lipoids.

Therefore a decision upon whether or not cholesterol is to be added to an antigen is of primary importance in relation to the standardization of technic. In my opinion *0.1 to 0.2 per cent cholesterol should be added and the hemolytic system adjusted accordingly to prevent nonspecific reactions which it is easily possible to do; under these conditions these extracts greatly increase the specific sensitiveness of the complement-fixation test for syphilis, which is highly desirable.*

#### METHODS FOR ESTABLISHING A STANDARD UNIT OF ANTIGEN

If the kind of antigen, method of titration and amount to use in complement-fixation tests could be agreed upon, a standard unit may be established by any one of the following procedures:

1. By using syphilitic serum as a standard and requiring an antigen to possess such antigenic sensitiveness as to fix complement with a certain amount of this standard serum. The problem then would be how to choose and keep this serum, what amount to use, how to replenish it from time to time to keep a uniform and standard unit and how it may be used in the titrations.
2. By using syphilitic spinal fluid in the same manner as serum.
3. By using an antigen as a standard and requiring new antigens to possess an acceptable degree of antigenic sensitiveness and certain freedom from anticomplementary and hemolytic activities. Under these conditions it would be necessary to determine what antigen to use, how it should be kept, how it may be replenished and yet maintain the standard unit and how it may be used in a series of titrations when testing new antigens.

My experiments have dealt with these three methods and are summarized under the following divisions:

- (a) Using serum and spinal fluid as standards.
- (b) Using antigens as standards.

## Part I

### USING SERUM AND SPINAL FLUID AS STANDARDS

*Selection.*—There is only one source of supply at the present time and that is the sera and spinal fluids of persons suffering with syphilis. Immune sera may be prepared by the prolonged immunization of rabbits with pure cultures of *T. pallidum* capable of fixing complement with tissue extract antigens but at the present time this method is not in use, although possible, if due care is exercised in excluding rabbits whose sera yield nonspecific reactions.

If human serum or spinal fluid is used how should it be selected? It should be highly polyvalent, that is, mixtures of sera or spinal fluids from a number of syphilitic persons in different stages of the disease.

So far I have seen no indisputable evidences of a *qualitative* difference in antibody in the different stages of syphilis in tests employing extracts reenforced with 0.2 per cent cholesterin and employing refrigerator primary incubation for 15 to 18 hours at 6 to 8° C.<sup>2</sup>; *quantitative* differences, however, have been plain, that is, the strength or degree of complement fixation bears a relationship to the stage of syphilis. For example, a reaction with serum during the primary stage of syphilis is seldom as strong quantitatively as during the secondary stage; however, the strength of a reaction does not necessarily bear a relationship to the clinical condition of an individual, very strong reactions being sometimes observed with the sera of persons apparently enjoying good health. This state is probably due to the activity of the spirochetes in tissues physiologically unimportant or, at least, not concerned with vital processes.

The main reason for using a mixture of sera or spinal fluids is to yield a serum or spinal fluid of average strength for titration. At least four to twelve *sterile* sera or spinal fluids should be used in making a mixture selected from those yielding moderately or strongly-positive reactions (for example, with 0.02 c.c. serum or

0.25 c.c. spinal fluid in my new test) and preferably from persons in different stages of syphilis. More may be used; probably the more used the better the mixture.

*Preservation.*—If serum or spinal fluid is selected how should it be preserved against bacterial contamination, the acquisition of anticomplementary activities and against loss of antibody or antigenic sensitiveness?

Undoubtedly bacterial contamination of either serum or spinal fluid ruins them for this purpose inasmuch as they become highly anticomplementary; furthermore they may become anticomplementary even under sterile conditions as previously discussed<sup>14</sup> when kept in a fluid state, although these developments are greatly retarded by keeping the serum or spinal fluid in a frozen state.

1. With the assistance of Dr. Berta Meine and Dr. Matsunami I have tried *drying sterile syphilitic sera* by various methods including that employed in the Hygienic Laboratory for the drying of antitoxins. When sera were quickly dried at a low temperature (0-6° C.) there was some loss of antibody and usually a distinct increase in anticomplementary activity as determined by titrations of fluid serum and solutions of corresponding amounts of the dried product (usually 0.078 to 0.158 gm. of dried serum corresponded to 1 c.c. of fluid serum) dissolved in water or saline solution. The main difficulty was in obtaining perfect solutions of the dried and powdered serum in the concentrations required.

When these sera were kept at 0-4° C. hermetically sealed in ampules, there were no appreciable further changes over periods of observation as long as two years, but I feel quite sure that the method is not adapted for the problem at hand, although at one time I felt quite confident of its success.

I have not worked with spinal fluids dried in this manner, or with fractions of syphilitic sera.

2. Additional experiments have been conducted with *sera dried in filter paper* after the method of Noguchi, but with unsatisfactory results principally due to a loss of antibody. Even rapid drying by fanning of sera absorbed in thick paper proved unsatisfactory because it was necessary to use too large amounts of paper for sufficient antibody yielding strong fixation reactions.

3. Many experiments have been conducted in *the preservation*

*of sera and spinal fluids with various antiseptics and kept in a refrigerator at 4 to 10° C.*

Most interest has been placed in the preservative properties of *glycerol* because of the satisfactory results reported by Ruediger. In our experience at least equal parts of serum and glycerol must be used for securing antiseptics (Table I); any concentration of glycerol below 40 per cent has not proved antiseptic for staphylococci.

TABLE I

THE GERMICIDAL AND ANTICOMPLEMENTARY ACTIVITIES OF STERILE GLYCERIN

PER CENT	GERMICIDAL	ANTICOMPLEMENTARY
1	Growth	—*
5	Growth	—
10	Growth	—
25	Growth	—
30	Growth	—
40	Antiseptic	—
50	Sterile	0.4
100	Sterile	0.2

\*—not anticomplementary in amounts from 0.1 to 0.6 c.c.

Unfortunately I have found mixtures of equal parts of serum and glycerol too anticomplementary for my hemolytic system; even after heating at 55° C. for one-half hour these mixtures were anticomplementary in amounts varying from 0.05 to 0.2 c.c. (Table II), the serum alone being free of anticomplementary properties in these amounts. Since it is advisable to use at least 0.05 c.c. serum corresponding to 0.1 c.c. of the mixture, glycerol preservation has not proved uniformly satisfactory. I may state, however, that after the initial changes occurring within the first few days, the antibody content and anticomplementary activity remain quite uniform for periods of six months to a year, as reported by Dr. Ruediger; the occasional mixture of serum and glycerol free of anticomplementary activity in amounts up to 0.3 c.c. in my hemolytic system (corresponding to 0.15 c.c. serum) could be used inasmuch as the close of 0.1 c.c. used (corresponding to 0.05 c.c. serum) would be at least one-third the anticomplementary unit.

Equal parts of fresh sterile spinal fluid and glycerol were usually anticomplementary in amounts varying from 0.2 to 0.5 c.c. (Table III) and since at least 0.2 c.c. spinal fluid corresponding

TABLE II

THE ANTICOMPLEMENTARY ACTIVITY OF MIXTURES OF SERUM AND STERILE GLYCERIN (MERCK'S BLUE LABEL)

SERUM-GLYCERIN	ANTICOMPLEMENTARY UNITS	
	UNHEATED	AFTER HEATING*
Unheated serum No. 1 + equal part gly.	0.05	0.1
Heated serum No. 1 + equal part gly.	0.2	0.2
Unheated serum No. 2 + equal part gly.	0.05	0.1
Heated serum No. 2 + equal part gly.	0.1	0.1
Sterile saline + equal part gly.	0.1	0.1

\*In a water-bath at 55° C. for thirty minutes.

TABLE III

THE ANTICOMPLEMENTARY ACTIVITY OF SPINAL FLUID PRESERVED WITH VARIOUS ANTISEPTICS AT 8° C.

PRESERVATION	PER CENT	1 DAY	1 WEEK	4 WEEKS	8 WEEKS
Phenol	0.5	—**	—	—	—
Phenol	0.25	—	—	—	—
Phenol	0.1	—	—	—	—
Tricresol	0.5	—	—	—	—
Tricresol	0.25	—	—	—	—
Tricresol	0.1	—	—	—	—
Formalin	0.5*	0.1***	0.1	0.1	0.1
Formalin	0.25	0.5	0.5	0.5	0.4
Formalin	0.1	—	—	—	—
Glycerin	50	0.2	0.4	0.3	0.3
Glycerin	25	0.4	0.5	0.5	0.4
Glycerin	10	—	—	—	—
Mercurophen	0.001	—	—	—	—
Mercurophen	0.0002	—	—	—	—
Mercurophen	0.0001	—	—	—	—

\* 0.1 c.c. pure formalin to 20 c.c. spinal fluid, etc.

\*\* — = not anticomplementary in amounts of 0.1 to 0.5 c.c. equivalent to 0.4 to 2.0 c.c. in terms of the original Wassermann test.

\*\*\* = smallest amounts beginning to inhibit hemolysis.

to 0.4 c.c. of the mixture should be used, it is only an occasional mixture that has proved acceptable.

Sterile sera preserved with *phenol* and *tricresol* in amounts from 0.1 to 0.5 per cent have not proved satisfactory; when kept at 4-8° C. they develop anticomplementary activity even though sterile, and the antilynsins are partly thermostabile or resistant to heat (55° C. for one-half hour).

With spinal fluids phenol and tricresol in dilutions varying from 1:20 to 1:100 and mercurophen in dilutions from 1:1000 to 1:10000 have proved much more satisfactory as shown in Table III. The materials were kept sterile and did not acquire increased anticomplemen-

tary activity over a period of eight weeks. *Formalin* however could not be used in strength over 1:100 (0.1 c.c. formalin to 9.9 c.c. spinal fluid).

4. *Sera and spinal fluids have been best preserved frozen solid.*—When kept in bulk repeated thawing and freezing have tended to hasten deterioration but when sera and spinal fluids have been placed in 1 c.c. ampules hermetically sealed and frozen solid they have been kept several months without increase of anticomplementary activity (Table IV). However, there is usually some deterioration of syphilis antibody after the first eight weeks (Table V). The results shown in Tables IV and V were observed with the hemolytic system and primary incubation adopted for the new complement-fixation test.<sup>2</sup>

TABLE IV  
THE ANTICOMPLEMENTARY ACTIVITY OF FROZEN SYPHILITIC SERUM

TESTS	AMOUNTS OF SERUM IN C.C.				
	0.05	0.1	0.2	0.3	0.4
At once	—*	—	—	2	2
1 week	—	—	—	2	2
2 weeks	—	—	—	1	1
3 weeks	—	—	—	2	2
4 weeks	—	—	—	2	2
8 weeks	—	—	—	2	2
6 weeks	—	—	—	1	1
10 weeks	—	—	—	2	1

\*\_ = complete hemolysis; 1 = slight inhibition of hemolysis; 2 = moderate inhibition of hemolysis.

TABLE V  
THE PRESERVATION OF SYPHILIS ANTIBODY IN FROZEN SERUM

TESTS	AMOUNTS OF SERUM IN C.C.							CONTROL 0.1
	0.1	0.05	0.025	0.0125	0.006	0.003	0.0015	
At once	++++	++++	++++	++++	++++	+++	+	—
1 week	++++	++++	++++	++++	++++	+++	+	—
2 weeks	++++	++++	++++	++++	++++	+++	+	—
3 weeks	++++	++++	++++	++++	++++	+++	±	—
4 weeks	++++	++++	++++	++++	++++	+++	—	—
6 weeks	++++	++++	++++	++++	++++	++	—	—
8 weeks	++++	++++	++++	++++	++++	++	—	—
10 weeks	++++	++++	++++	++++	+++	+	—	—

Sterile sera and spinal fluids kept in this manner without the addition of any preservative have yielded best results of the methods included in this study for the preservation of serum; the dis-

advantages are the chances of ampules breaking and the necessity for maintaining a refrigerator or a "Frigo" at a sufficiently low temperature to keep the products frozen solid.

*Serum Versus Spinal Fluid for Standards.*—The question now arises which is better, frozen serum or frozen spinal fluid for the purpose of maintaining a unit of measure for the titration of antigen?

From the standpoint of preservation, spinal fluid has proved superior to serum because it was less likely to develop anticomplementary properties while the deterioration of syphilis antibody was no greater than that occurring in serum.

Comparative tests have shown that mixtures of spinal fluids are from 10 to 20 times weaker in fixing power than mixtures of syphilitic sera, that is to say, from 0.025 c.c. to 0.05 c.c. of spinal fluid equaled 0.001 to 0.006 c.c. of serum in complement-fixing power when tested at the same time, with the same antigen and same general technic.<sup>2</sup>

The disadvantages attending the use of spinal fluid were: 1. The great variation in amounts of syphilis antibody in spinal fluids from different syphilitics varying from a very large amount in paresis, to much smaller amounts in cases of secondary and tertiary syphilis with no discernible symptoms of involvement of the central nervous system; 2. The difficulty of obtaining sufficient amounts from many different cases of syphilis to permit the use of a mixture tending to give a fair and fairly uniform content of antibody.

#### THE USE OF A FROZEN SERUM AND SPINAL FLUID FOR ESTABLISHING AND MAINTAINING A UNIT OF MEASURE FOR THE TITRATION OF ANTIGEN

Having established that serum and spinal fluid are best preserved frozen solid with or without the addition of 0.1 per cent phenol or tricresol, a large amount of study has been given to the determination of the practical value of carrying frozen serum as a standard unit for titrating antigen.

Having determined the smallest amount of a mixture of twelve syphilitic sera giving a ++++ reaction with a cholesterolized and lecithinized alcoholic extract of beef heart<sup>5</sup> five units of serum were used in titrations for determining the antigenic units of different extracts with these results:

Unit of cholesterolized alc. ext. beef heart = 0.5 c.c. of 1:600  
Unit of a cholest. and lecithin. alc. ext. beef heart = 0.5 c.c. of 1:900  
Unit of a plain alc. ext. beef heart = 0.5 c.c. of 1:300  
Unit of a plain alc. ext. syph. liver = 0.5 c.c. of 1:100  
Unit of an extract of acetone insoluble lipoids = 0.5 c.c. of 1:500

Ten units of each of these five antigens were then used in quantitative complement-fixation tests with each of five sera from syphilitic persons. With the 0.1 c.c. amounts of the different sera the five antigens yielded identical ++++ reactions; with the 0.02, .002 and 0.001 amounts of each serum, however, the reactions varied, being strongest with the cholesterolized and lecithinized alcoholic extracts of beef heart and weakest with the alcoholic extract of syphilitic liver. For this reason *absolute uniformity in results cannot be expected in quantitative tests with different kinds of antigen even when these have been titrated with the same serum at the same time and under identical conditions and used in a dose of ten units for conducting complement-fixation tests with syphilitic sera.* This fact has been previously mentioned and discussed and is the basis of my conviction that in the standardization of the complement-fixation test for syphilis there must be first an agreement on the *kind of antigen.* However, in qualitative tests, that is, tests using one dose of serum, the differences among antigens are not nearly so evident as in quantitative tests.

Additional experiments with frozen serum were now conducted with a single kind of antigen, namely, cholesterolized and lecithinized alcoholic extracts of beef heart; similar experiments were also conducted with frozen spinal fluids. These experiments have shown that a mixture of syphilitic sera or spinal fluids frozen solid for preservation may be successfully used for the purpose of establishing and maintaining a unit of measure for titrating *antigens of the same kind* according to the following technic:

1. The hemolytic system and primary incubation are the same as described for the titration of antigen in the succeeding paper<sup>2</sup>; these details are omitted here for brevity.

2. A mixture of twelve or more carefully picked syphilitic sera yielding ++++ reactions in the new test in amounts of 0.02 c.c. or less are mixed, distributed in 1 c.c. ampules and kept in a frozen



state, or a mixture of spinal fluids yielding ++++ reactions in amounts of 0.25 c.c. or less are mixed and kept in the same manner.

3. The smallest amount of this serum giving a ++++ reaction with ten units of good and well tried antigen is determined in a titration employing the following amounts of serum thawed and heated at 55° C. for fifteen minutes: 0.02, 0.015, 0.01, 0.009, 0.008, 0.007, 0.006, 0.005, 0.004, 0.003, 0.002 and 0.001 c.c.; this amount of serum is called the *fixing unit of serum*. To be satisfactory this unit must be 0.02 c.c. or less.

If spinal fluid is used it should be titrated unheated in amounts of 0.2, 0.15, 0.1, 0.09, 0.08, 0.07, 0.06, 0.05, 0.04, 0.03, 0.02, and 0.01 c.c. and the smallest amount yielding a ++++ reaction designated as the *fixing unit of spinal fluid*. To be satisfactory this unit must be 0.2 c.c. or less.

At the same time the anticomplementary activity of the serum or spinal fluid should be determined and to be satisfactory a serum should be free of anticomplementary activity in amounts up to 0.3 c.c. and spinal fluid up to 1.5 c.c.

4. The serum or spinal fluid may now be used for the titration of antigens for a period of at least two months; sometimes for much longer periods before deterioration in fixability becomes apparent. If kept frozen solid there is no increase in anticomplementary activity.

*When titrating the antigenic activity of a new antigen five fixing units of serum or spinal fluid are used.* The new antigen is also titrated for anticomplementary and hemolytic activity. The technic is exactly the same as described<sup>2</sup> except that five fixing units of serum are used instead of the arbitrary amount of syphilitic serum (0.05 c.c.) advised in this paper for the titration of antigen.

5. The new antigen is then used in a dose of ten units for conducting complement-fixation tests for syphilis providing this dose is at least six times less than the anticomplementary and hemolytic units.

6. At the end of two months or when the standard serum or spinal fluid shows the earliest evidences of deterioration, it is necessary to prepare another serum or spinal fluid and adjust its fixing unit to the fixing unit of the first serum or spinal fluid. This has been accomplished as follows:

7. Both the standard serum and new serum are titrated for their

fixing units with ten units of a good antigen (always the same kind of antigen). It is assumed that the standard serum has practically unaltered fixing power so that if it yields a different unit, the change in fixing unit is due to the antigen.

8. If the fixing unit of the first or standard serum is now *more* than formerly this amount of serum becomes the numerator of a fraction of which the former unit becomes the denominator and the fixing unit of the second serum adjusted to the original standard unit as per this example:

Fixing unit of standard serum = 0.005 c.c.

Fixing unit of standard serum two months later = 0.008 c.c.

Fixing unit of new serum = 0.004 c.c.

$$\frac{.008 \text{ c.c.}}{.005 \text{ c.c.}} = 1.66$$

$0.004 \text{ c.c.} \times 1.66 = .0066 \text{ c.c.}$  (the fixing unit of the new or second serum for the succeeding two months).

If, however, the fixing unit of the standard serum is a smaller amount of serum in this titration owing to the use of a more sensitive antigen the calculation is made as follows:

Fixing unit of standard serum = 0.005 c.c.

Fixing unit of standard serum two months later = 0.003 c.c.

Fixing unit of new serum = 0.002 c.c.

$$\frac{.005 \text{ c.c.}}{.003 \text{ c.c.}} = 1.66$$

$0.002 \text{ c.c.} \times 1.66 = 0.0033 \text{ c.c.}$  (the fixing unit of the new serum for the succeeding two months).

If spinal fluid is being used instead of serum, the fixing unit of a new spinal fluid is adjusted to the former fluid in the same manner.

9. The new or second serum or spinal fluid now becomes the standard and at the end of two months a third serum or spinal fluid is adjusted to it in the same manner as described, the system being kept in continuous operation.

## Part Two

### THE USE OF ANTIGEN FOR ESTABLISHING AND MAINTAINING A UNIT OF MEASURE FOR THE TITRATION OF ANTIGEN

Since it is troublesome to maintain a standard serum or spinal fluid in a frozen state and since antigens frequently keep for

months and even years practically unchanged, I have sought to determine the possible value of maintaining an antigen as a standard unit of measure for the titration of antigens.

*Selection and Preservation of Antigen.*—After numerous experiments with plain and cholesterolized extracts of human and beef heart and alcoholic extracts of syphilitic liver, I have reached the conclusion that acetone insoluble lipoids made from beef heart muscle and preserved in pure acetone or dried in vials, are best for this purpose.

While it is true that alcoholic extracts frequently keep unchanged for long periods of time after they have "ripened" yet they may change suddenly and we have no knowledge of these changes which are principally in the nature of an increase of anti-complementary activity. However, the acetone insoluble lipoids have been kept in acetone for long periods of time and 0.3 gm. carefully weighed, dissolved in 2 c.c. of ether and 9 c.c. of acetone-free methyl alcohol yields an extract which maintains its antigenic, anticomplementary and hemolytic properties remarkably well. Simple alcoholic extracts of beef heart, and especially these extracts reenforced with 0.2 per cent cholesterol, have also kept practically unchanged for many months, but in my experience the acetone insoluble lipoids are somewhat more reliable and worth the extra work and expense involved.

These acetone insoluble lipoids are best made according to the method of Noguchi and Bronfenbrenner from *fresh* beef heart;\* after precipitation with acetone I redissolve the precipitates in ether and reprecipitate with acetone. After allowing this precipitate to settle the supernatant acetone is decanted, the lipoids rolled into a mass and kept in the same acetone in an air tight vessel in a refrigerator.

Numerous experiments have also been conducted with various antigens dried in filter paper but without success. However, cholesterolized and lechithinized alcoholic extracts of beef heart, alcoholic extracts of beef heart reenforced with 0.2 per cent cholesterol, and 3 per cent solutions of acetone insoluble lipoids dissolved in ether have been kept in fairly successful manner by placing 5 c.c. of antigen in weighing vials fitted with ground-glass stoppers and fanning until dry. These dishes were then kept at room temperature in a dry at-

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\*Liver (human or beef) yields larger residues but the lipoids are likely to be inferior in antigenic activity.

mosphere and antigens subsequently prepared by dissolving the residue in a vial in alcohol.

During the process of drying, an antigen sometimes acquires a slightly increased anticomplementary activity, but the antigenic activity has remained unchanged in our experiments.

*The Use of Acetone Insoluble Lipoids Kept in Acetone or Dried Cholesterolized and Lecithinized Alcoholic Extracts for Establishing and Maintaining a Unit of Measure for the Titration of Antigen.*

At this time I am unable to state which antigen is the better; both have yielded good and satisfactory results.

1. When the acetone insoluble lipoids are used the mass is removed from the acetone and briefly fanned; 0.3 gm. is carefully weighed out on a piece of tin foil and the whole placed in a small cylinder fitted with a ground-glass stopper. 2 c.c. of highest grade ether are added and the residue dissolved; 9 c.c. of best grade acetone-free methyl alcohol are now added and well shaken. The extract is used unfiltered.

2. If dried antigen is to be used 5 c.c. amounts are placed in small vials with ground-glass stoppers and fanned to dryness. These are kept at room or refrigerator temperature. When used 5 c.c. of absolute ethyl alcohol are carefully added to a vial and the residue dissolved; the extract is used unfiltered.\*

3. The antigen is now titrated for antigenic, anticomplementary and hemolytic activity exactly as described in a succeeding paper;<sup>2</sup> the smallest amount giving a ++++ reaction is called the antigenic unit. This unit has kept unchanged for at least six months with both acetone insoluble lipoids and dried.

4. When a new antigen is to be titrated and adjusted to this standard antigen, the titrations are conducted as follows:

(a) A fresh syphilitic serum (preferably a mixture of several sera) is heated at 55° C. for fifteen minutes and used in amounts of 0.02, 0.015, 0.01, 0.009, 0.008, 0.007, 0.006, 0.005, 0.004, 0.003, 0.002 and 0.001 c.c. with ten units of the standard or preserved antigen to determine the fixing unit or smallest amount of serum giving a ++++ reaction, the hemolytic system and technic being that described.<sup>2</sup>

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\*This refers to use of a cholesterolized and lecithinized alcoholic extract of heart muscle. If dried acetone insoluble lipoids are used 0.3 gm. dissolved in 5 c.c. of ether should be placed in each vial and fanned to dryness. When used the residue is dissolved by adding 2 c.c. of ether followed by 9 c.c. of acetone-free methyl alcohol; the extract is used unfiltered.

(b) The new antigen is titrated for hemolytic and anticomplementary activity as described.<sup>2</sup>

(c) The standard antigen and new antigen are now titrated for antigenic activity using ten fixing units of the syphilitic serum. Each antigen is used in amounts of 0.5 c.c. of eighteen dilutions, from 1:100 to 1:1800. The smallest amount of each antigen giving a ++++ reaction is the antigenic unit. Of course the unit of standard antigen is likely to vary from its former unit because of a difference in the serum, but adjustment is made according to the following example:

Standard antigenic unit 0.5 c.c. of 1:600 (0.00083 c.c.)

Unit of standard antigen in new titration 0.5 c.c. of 1:300 (0.0015 c.c.)

Unit of new antigen 0.5 c.c. of 1:900 (0.00055 c.c.)

$$\frac{0.00083 \text{ c.c.}}{0.0015 \text{ c.c.}} \times \frac{0.00055 \text{ c.c.}}{1} = 0.0003 \text{ c.c. or } 0.5 \text{ of } 1:1666$$

dilution of the new antigen is equal to the standard unit and would be the new standard unit; ten units or 0.5 c.c. of 1:166 would be used in conducting complement-fixation tests for syphilis.

Second example:

Standard antigenic unit 0.5 c.c. of 1:600 (0.00083 c.c.)

Unit of standard antigen in new titration 0.5 c.c. of 1:800 (0.000625 c.c.)

Unit of new antigen 0.5 c.c. of 1:700 (0.000715 c.c.)

$$\frac{0.00083 \text{ c.c.}}{0.000625 \text{ c.c.}} \times \frac{0.000715 \text{ c.c.}}{1} = 0.00095 \text{ c.c. or } 0.5 \text{ c.c. of } 1:526$$

dilution of the new antigen is equal to the standard unit of 0.5 c.c. of 1:600 and could be used for the new standard antigen if the older antigen was exhausted or spoiled. In complement-fixation tests the new antigen would be used in dose of ten units or 0.5 c.c. of 1:53 if this amount were at least six times or more under the anticomplementary and hemolytic units.

5. In this manner new standard antigens have been adjusted as the original and preceding antigens were exhausted, the unit being constantly adjusted to the original.

Likewise new antigens of cholesterolized and lecithinized alcoholic extracts designed for complement-fixation tests, have been adjusted to a constant standard of antigenic activity.

## SUMMARY

1. Different kinds of antigen titrated by a uniform method and used in a dose of ten antigenic units in a *qualitative* complement-fixation test employing cold primary incubation yield fairly uniform results insofar as positive or negative reactions are concerned. In *quantitative* tests, however, there is considerable difference in that antigens containing cholesterol are more sensitive.

2. Of primary importance therefore in the standardization of the Wassermann test is a decision upon the *kind* and *amount* of antigen and *kind* and *duration* of primary incubation, to employ.

3. With these factors settled different serologists working with the same kind of antigen and the same technic may secure remarkably uniform results by making and titrating their own antigens.

4. It is possible, however, to establish in a central laboratory a standardized and uniform unit for the titration of antigen by any one of the following three methods which are described in detail:

(a) Frozen syphilitic serum or spinal fluid may be maintained as a unit of measure.

(b) Acetone insoluble lipoids preserved in acetone may be maintained as a unit of measure.

(c) Dried antigens (acetone insoluble lipoids or cholesterolized and lecithinized alcoholic extracts of beef heart) may be maintained as a unit of measure.

5. Of these three methods (b) and (c) have proved most satisfactory.

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## STUDIES IN THE STANDARDIZATION OF THE WASSER- MANN REACTION, XXXI\*

### THE NEW COMPLEMENT-FIXATION TEST FOR SYPHILIS CONDUCTED WITH ANTIHUMAN, ANTICHICKEN AND ANTIOX HEMOLYTIC SYSTEMS

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(Received for publication, March 12, 1921.)

A large number of comparative tests have shown that the presence of natural antishoop hemolysin in guinea pig serum complement and in the sera of persons examined by the *new complement-fixation test* for syphilis<sup>1</sup> has practically no influence upon the sensitiveness of the reaction. Indeed as shown in this communication, tests conducted according to the new technic but with an antihuman hemolytic system have frequently yielded somewhat less sensitive reactions than observed in duplicate tests conducted with the antishoop hemolytic system.

In some laboratories however, sheep blood is not available, and for this primary reason we have determined under what conditions the corpuscles of human beings, chickens and cattle may be substituted in the new test to yield the most sensitive and specific reactions similar to those resulting with the antishoop hemolytic system.

*Contrary to general impressions the substitution of one hemolytic system for another is not as simple as it appears when considered from the standpoint of excellence in results; substitution usually requires a change in the dilution and amount of complement required and this introduces a degree of variation in the complement-fixation reactions.*

#### HEMOLYTIC SYSTEMS

As stated above we have made comparative studies of the new test conducted with antishoop, antiox, antihuman and antichicken hemolytic systems. Of these four hemolysins, that for sheep cells is

\*From the Dermatological Research Laboratories of Philadelphia. Investigation aided by funds accruing from the preparation of arsphenamine. I am indebted to Miss Rule, Miss Trist and Miss Yagle for assistance in this work.

easiest to prepare by immunization of rabbits and yields the most powerful hemolysin; that for beef corpuscles comes next while the hemolysins for human and chicken corpuscles are far more difficult of preparation, these cells being more toxic for rabbits and the immune sera being much less hemolytic.<sup>2</sup>

Rabbits immunized with five intravenous injections of sheep corpuscles in dose of 5 c.c. of 10 per cent suspensions every five days usually yield sera in which the unit according to the new technic is 0.5 c.c. of 1:2000 or higher. With the same technic of immunization with beef corpuscles the unit of hemolysin is about 1:200 or higher and sometimes it is necessary to give more than five injections to obtain a serum of this strength. Immunization of rabbits with human and chicken corpuscles is probably best conducted by giving daily intravenous injections of 1 c.c. of 10 per cent suspensions; after three or four weeks of injections the sera usually yield a unit of 0.5 c.c. of 1:40 or higher when titrated according to the new technic but in which the complement is used 1:10 instead of 1:30. So far we have not been able to produce these hemolysins sufficiently powerful to work in the new test with 1:30 complement, as is used with the antisheep system.

Experience has shown that *tests conducted with antisheep and antiox hemolytic systems are slightly more sensitive than tests conducted with the antihuman and antichicken systems.* We believe that *these differences are due to the complement and not to natural hemolysins in human sera.* It appears to be a fundamental principle that *the higher the dilution of complement, that is, the smaller the amount of serum we may use the more sensitive are the complement-fixation reactions.* The difficulties encountered in the preparation of antihuman and antichicken hemolysins are such that it is usually necessary to use the complement diluted 1:5 or 1:10 and *these larger amounts of guinea pig serum complement reduce the sensitiveness of reactions with the new technic probably by the introduction of serum proteins interfering with specific complement-fixation.* The presence or absence of natural hemolysins in the complement serum appear to be of much lesser importance because the results are the same regardless of the presence or absence of these substances in the complement or patients' sera.



TECHNIC OF THE NEW TEST WITH ANTIOX, ANTIHUMAN AND  
ANTICHICKEN HEMOLYTIC SYSTEMS

The technic is exactly as described<sup>1</sup> for the antish sheep system except the dilution of complement employed; experience has shown that these dilutions should be as follows:

1:20 or 1:30 complement for the antiox system, *preferably 1:30*.

1:15 or 1:10 complement for the antihuman and antichicken systems, *preferably 1:10*.

If the antiox system is adopted an effort should be made to prepare hemolysin of such strength that 0.5 c.c. of a 1:1000 dilution will completely hemolyze 0.5 c.c. of 2 per cent washed beef corpuscles with 0.3 c.c. of 1:30 mixed guinea pig complement in one hour in a water-bath at 38° C.

If the antihuman or antichicken systems are adopted the hemolysins should be of such strength that at least 0.5 c.c. of a 1:40 dilution will give complete hemolysis of 0.5 c.c. of 2 per cent suspensions of cells with 0.3 c.c. of 1:10 complement in one hour in a water-bath at 38° C. It may be necessary to use 1:5 complement because of weak hemolysins but it is advisable to continue the immunization of rabbits until the hemolytic sera are sufficiently powerful to act satisfactorily with 1:10 complement.

*Whatever the system may be it is necessary to titrate the antigen with that system;* for example, the unit of antigen titrated with the antish sheep system is much different from that titrated with the antihuman system; the differences are due to the different dilutions of complement.

*If antigen is titrated with 1:30 complement as described for the antish sheep system, the unit is satisfactory for the antiox system using 1:30 complement but not if it is necessary to use 1:20 complement;* if the hemolysin demands the use of 1:20 complement then the antigen must be titrated with this dilution of complement.

Tables I and II show the influence upon the results of antigen titrations with different strengths of complement in an antish sheep hemolytic system. For example, the antigenic unit of a cholesterolized and lecithinized alcoholic extract of beef heart<sup>3</sup> was 0.5 c.c. of 1:1200 with 1:30 complement, 1:1000 with 1:20 complement and 1:800 with 1:10 complement. Likewise there is a difference in the anticomplementary units of antigen according to the dilution of

TABLE I  
THE INFLUENCE OF DILUTION OF COMPLEMENT IN AN ANTISHEEP HEMOLYTIC SYSTEM UPON THE TITRATION OF ANTIGENS FOR ANTIGENIC ACTIVITY

ANTIGENS	COMPLEMENT 1:10; 0.5 C.C. ANTIGEN:										COMPLEMENT 1:20; 0.5 C.C. ANTIGEN:										COMPLEMENT 1:30; 0.5 C.C. ANTIGEN:									
	1:100	1:200	1:300	1:400	1:500	1:600	1:800	1:1000	1:1200	1:1600	1:100	1:200	1:300	1:400	1:500	1:600	1:800	1:1000	1:1200	1:1600	1:100	1:200	1:300	1:400	1:500	1:600	1:800	1:1000	1:1200	1:1600
	4*	4	4	4	4	4	4	3	1	1	4	4	4	4	4	4	4	4	4	3	2	4	4	4	4	4	4	4	4	3
Cholest. and lecithin. alc. ext. beef heart.....	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	3
Cholest. alc. ext. beef heart.....	4	4	4	3	1	—	—	—	—	—	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
Plain alc. ext. beef heart.....	4	2	1	—	—	—	—	—	—	—	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
Acet. insol. lipoids.....	4	4	3	1	—	—	—	—	—	—	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4

4 = + + + + +; 3 = + + + +; 2 = + +; 1 = +; — = complete hemolysis.

TABLE II  
THE INFLUENCE OF DILUTION OF COMPLEMENT IN AN ANTISHEEP HEMOLYTIC SYSTEM UPON THE TITRATION OF ANTIGEN FOR ANTICOMPLEMENTARY ACTIVITY

ANTIGENS	COMPLEMENT 1:10; 0.5 C.C. ANTIGEN:										COMPLEMENT 1:20; 0.5 C.C. ANTIGEN:										COMPLEMENT 1:30; 0.5 C.C. ANTIGEN:									
	1:4	1:5	1:6	1:8	1:10	1:12	1:16	1:20	1:24	1:32	1:4	1:5	1:6	1:8	1:10	1:12	1:16	1:20	1:24	1:32	1:4	1:5	1:6	1:8	1:10	1:12	1:16	1:20	1:24	1:32
Cholest. and lecithin. alc. ext. beef heart.....	4*	3	—	—	—	—	—	—	—	—	4	4	3	—	—	—	—	—	—	—	4	4	4	1	—	—	—	—	—	—
Cholest. alc. ext. beef heart.....	4	4	2	—	—	—	—	—	—	—	4	4	4	3	1	—	—	—	—	—	4	4	4	4	2	1	—	—	—	—
Plain alc. ext. beef heart.....	4	4	4	1	—	—	—	—	—	—	4	4	4	2	1	—	—	—	—	—	4	4	4	4	3	2	1	—	—	—
Acet. insol. lipoids.....	4	4	2	—	—	—	—	—	—	—	4	4	4	3	1	—	—	—	—	—	4	4	4	4	4	1	—	—	—	—

\* 4 = complete inhibition of hemolysis; 3 = moderate inhibition of hemolysis; 2 = weak inhibition of hemolysis; 1 = weak inhibition of hemolysis; — = no inhibition of hemolysis.

TABLE III  
THE TITRATION OF EXTRACTS FOR ANTIGENIC ACTIVITY BY THE NEW TECHNIC EMPLOYING DIFFERENT HEMOLYTIC SYSTEMS

ANTIGENS	ANTISHEEP SYSTEM **, 0.5 C.C. OF ANTIGEN:										ANTIOX SYSTEM ***, 0.5 C.C. OF ANTIGEN:										ANTIHUMAN SYSTEM ****, 0.5 C.C. OF ANTIGEN:									
	1:100	1:200	1:300	1:400	1:500	1:600	1:800	1:1000	1:1200	1:1600	1:100	1:200	1:300	1:400	1:500	1:600	1:800	1:1000	1:1200	1:1600	1:100	1:200	1:300	1:400	1:500	1:600	1:800	1:1000	1:1200	1:1600
Cholest. and lecithin. alc. ext. beef heart.....	4*	4	4	4	4	4	4	4	3	2	4	4	4	4	3	3	2	2	—	—	4	4	2	—	—	—	—	—	—	—
Cholest. alc. ext. beef heart.....	4	4	4	4	4	3	2	—	—	—	4	4	3	3	1	—	—	—	—	—	4	4	1	—	—	—	—	—	—	—
Plain alc. ext. beef heart.....	4	4	4	3	—	—	—	—	—	—	4	4	3	3	1	—	—	—	—	—	2	1	—	—	—	—	—	—	—	—
Acet. insol. lipoids.....	4	4	4	4	4	3	3	1	—	—	4	4	4	3	3	2	—	—	—	—	4	1	—	—	—	—	—	—	—	—

\* 4 = + + + +; 3 = + + +; 2 = + +; 1 = +; — = negative.

\*\* Complement 1:30; \*\*\* Complement 1:15; \*\*\*\* Complement 1:10.

TABLE IV  
THE TITRATION OF EXTRACTS FOR ANTICOMPLEMENTARY ACTIVITY BY THE NEW TECHNIC EMPLOYING DIFFERENT HEMOLYTIC SYSTEMS

ANTIGENS	ANTISHEEP SYSTEM **, 0.5 C.C. OF ANTIGEN:							ANTIOX SYSTEM ***, 0.5 C.C. OF ANTIGEN:							ANTIHUMAN SYSTEM ****, 0.5 C.C. OF ANTIGEN:													
	1:4	1:5	1:6	1:8	1:10	1:12	1:24	1:32	1:4	1:5	1:6	1:8	1:10	1:12	1:16	1:20	1:24	1:32	1:4	1:5	1:6	1:8	1:10	1:12	1:16	1:20	1:24	1:32
Cholest. and lecithin. alc. ext. beef heart.....	3*	2	1	—	—	—	—	—	2	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Cholest. alc. ext. beef heart.....	4	3	3	2	2	1	—	—	4	3	2	1	—	—	—	—	—	—	—	2	1	1	—	—	—	—	—	—
Plain alc. ext. beef heart.....	4	3	2	—	—	—	—	—	3	2	1	—	—	—	—	—	—	—	—	2	1	—	—	—	—	—	—	—
Acet. insol. lipoids.....	3	3	3	2	1	—	—	—	3	3	3	1	—	—	—	—	—	—	—	2	1	—	—	—	—	—	—	—

\* 4 = complete inhibition of hemolysis (100%); 3 = moderate inhibition of hemolysis (75%); 2 = weak inhibition of hemolysis (50%); 1 = very weak inhibition of hemolysis (25%); — = complete hemolysis.

\*\* Complement 1:30; \*\*\* Complement 1:15; \*\*\*\* Complement 1:10.

TABLE V

SUMMARY SHOWING THE INFLUENCE OF DILUTION OF COMPLEMENT UPON THE RESULTS OF TITRATIONS OF ANTIGENS FOR ANTIGENIC ACTIVITY

ANTIGENS	ANTISHEEP; COMPLEMENT:		ANTITOX; COMPLEMENT:		ANTHUMAN; COMPLEMENT:	
	1:10	1:20	1:30	1:10	1:20	1:30
Cholest. and lecithin. alc. extract	1:800*	1:1000	1:1600	1:600	1:800	1:1000
Cholest. alcoholic extract	1:300	1:500	1:500	1:300	1:400	1:500
Plain alcoholic extract	1:100	1:400	1:500	1:100	1:200	1:400
Acetone insoluble lipoids	1:200	1:500	1:600	1:100	1:400	1:500

\*The antigenic units, that is, 0.5 c.c. of the highest dilutions giving +++ reactions.

\*\* - = not antigenic in 0.5 c.c. of 1:100.

TABLE VI

SUMMARY SHOWING THE INFLUENCE OF DILUTION OF COMPLEMENT UPON THE RESULTS OF TITRATIONS OF ANTIGENS FOR ANTIGENIC ACTIVITY

ANTIGENS	ANTISHEEP; COMPLEMENT:		ANTITOX; COMPLEMENT:		ANTHUMAN; COMPLEMENT:	
	1:10	1:20	1:30	1:10	1:20	1:30
Cholest. and lecithin. alc. extract	1:6*	1:6	1:6	1:4	1:5	1:6
Cholest. alcoholic extract	1:6	1:10	1:12	1:5	1:8	1:10
Plain alcoholic extract	1:8	1:10	1:12	1:6	1:6	1:8
Acetone insoluble lipoids	1:6	1:10	1:10	1:5	1:6	1:8

\*The anticomplementary units, that is, 0.5 c.c. of the highest dilutions producing slight inhibition of hemolysis.

complement employed. This antigen was anticomplementary with 1:30 complement in dose of 0.5 c.c. of 1:6; with 1:20 complement the unit was also 0.5 c.c. of 1:6, while 0.5 c.c. of 1:5 with 1:10 complement.

Tables III and IV show the very remarkable differences in the results of titrations of four different antigens with antishoop, antiox and antihuman hemolytic systems employing 1:30, 1:15 and 1:10 dilutions of complement respectively. These titrations were made at the same time, with the same sera and under identical conditions.

As shown in Table III the antigenic unit of the cholesterolized and lecithinized alcoholic extract of beef heart was 0.5 c.c. of 1:1000 with the antishoop system (1:30 complement), 0.5 c.c. of 1:400 with the antiox system (1:15 complement) and 0.5 c.c. of 1:200 with the antihuman system (1:10 complement). If for example ten units according to the antishoop system (0.5 c.c. of 1:100) were used with the antihuman system this amount would fall short of that required being only two units for the antihuman system.

A similar influence is exerted upon the anticomplementary activities of different antigens. For example, the cholesterolized and lecithinized alcoholic extract of beef heart was anticomplementary in 0.5 c.c. of 1:6 with the antishoop system (1:30 complement), 0.5 c.c. of 1:5 with the antiox system (1:15 complement) but not anticomplementary at all in 0.5 of 1:4 with the antihuman system (1:10 complement).

Tables V and VI present a summary of the results of titrations of four antigens with different dilutions of complement in antishoop, antiox and antihuman hemolytic systems. An inspection of these tables shows at a glance *that irrespective of the hemolytic system the dilution of complement, that is, the amount of complement employed, profoundly alters the antigenic and anticomplementary values of antigens and that if the substitution of one hemolytic system for another calls for a change in the amount of complement the antigen must be titrated accordingly.*

Even when a hemolytic system is adjusted to different dilutions of complement and the antigen is titrated with each dilution and used in doses of ten antigenic units according to each titration with the technic of the new test, the results are not identical; *as a general rule the tests are more sensitive with the higher than with the lower dilutions of complement.*

TABLE VII

THE INFLUENCE OF DILUTION OF COMPLEMENT IN AN ANTISHEEP HEMOLYTIC SYSTEM UPON THE SENSITIVENESS OF COMPLEMENT-FIXATION REACTIONS

SERA	COMPLEMENT 1:10; SERA:					COMPLEMENT 1:20; SERA:					COMPLEMENT 1:30; SERA:				
	0.1	0.02	0.004	0.002	0.001	0.1	0.02	0.004	0.002	0.001	0.1	0.02	0.004	0.002	0.001
1	4	3	-	-	-	4	4	-	-	-	4	4	1	-	-
2	4	2	-	-	-	4	3	-	-	-	4	4	-	-	-
3	4	2	-	-	-	4	3	-	-	-	4	4	1	-	-
4	4	1	-	-	-	4	1	-	-	-	4	3	-	-	-

TABLE VIII

THE INFLUENCE OF DILUTION OF COMPLEMENT IN AN ANTIOX HEMOLYTIC SYSTEM UPON THE SENSITIVENESS OF COMPLEMENT-FIXATION REACTIONS

SERA	COMPLEMENT 1:10; SERA:					COMPLEMENT 1:20; SERA:					COMPLEMENT 1:30; SERA:				
	0.1	0.02	0.004	0.002	0.001	0.1	0.02	0.004	0.002	0.001	0.1	0.02	0.004	0.002	0.001
1	4	3	-	-	-	4	4	-	-	-	4	4	-	-	-
2	2	1	-	-	-	4	2	-	-	-	4	3	-	-	-
3	4	-	-	-	-	4	3	-	-	-	4	4	-	-	-
4	2	-	-	-	-	4	2	-	-	-	4	3	-	-	-

TABLE IX

THE INFLUENCE OF DILUTION OF COMPLEMENT IN AN ANTIHUMAN HEMOLYTIC SYSTEM UPON THE SENSITIVENESS OF COMPLEMENT-FIXATION REACTIONS

SERA	COMPLEMENT 1:1½; SERA:					COMPLEMENT 1:5; SERA:					COMPLEMENT 1:10; SERA:				
	0.1	0.02	0.004	0.002	0.001	0.1	0.02	0.004	0.002	0.001	0.1	0.02	0.004	0.002	0.001
1	1	-	-	-	-	2	-	-	-	-	3	1	-	-	0.1
2	2	-	-	-	-	2	-	-	-	-	4	1	-	-	-
3	2	-	-	-	-	3	-	-	-	-	4	1	-	-	-
4	1	-	-	-	-	3	-	-	-	-	4	1	-	-	-

TABLE X

COMPARATIVE SENSITIVENESS OF REACTIONS OBSERVED WITH THE NEW TECHNIC EMPLOYING DIFFERENT HEMOLYTIC SYSTEMS

CASE	ANTISHEEP SYSTEM **					ANTIOX SYSTEM **					ANTIHUMAN SYSTEM ***					ANTIHLICKEN SYSTEM ***				
	0.1	0.02	0.004	0.002	0.001	0.1	0.02	0.004	0.002	0.001	0.1	0.02	0.004	0.002	0.001	0.1	0.02	0.004	0.002	0.001
1	4*	4	4	3	3	4	4	4	3	2	4	4	3	1	-	4	4	3	1	-
3	4	4	4	3	-	4	4	4	2	-	4	4	2	1	-	4	4	3	1	-
6	4	4	4	2	-	4	4	4	2	-	4	4	3	-	-	4	4	3	-	-
8	4	4	3	-	-	4	4	3	-	-	4	4	2	-	-	4	4	3	-	-
9	4	4	4	2	-	4	4	4	1	-	4	4	1	-	-	4	4	3	-	-
10	4	4	4	1	-	4	4	3	1	-	4	4	4	1	-	4	4	4	2	-
12	4	4	4	3	2	4	4	4	2	1	4	4	3	1	-	4	4	3	1	-
13	4	4	4	4	3	4	4	4	4	2	4	4	4	3	1	4	4	4	3	1
14	4	4	4	4	1	4	4	4	4	2	4	4	4	4	2	4	4	4	4	3
15	4	4	2	-	-	4	4	1	-	-	4	4	3	-	-	4	4	3	-	-

\* 4 = ++++; 3 = +++; 2 = ++; 1 = +; - = negative.

\*\* Complement 1:30; \*\*\* Complement 1:5.

TABLE XI  
COMPARATIVE SENSITIVENESS OF REACTIONS OBSERVED WITH THE NEW TECHNIC EMPLOYING DIFFERENT HEMOLYTIC SYSTEMS

CASE	ANTISHEEP SYSTEM**					ANTIOX SYSTEM***					ANTI HUMAN SYSTEM****				
	0.1	0.02	0.004	0.002	0.001	0.1	0.02	0.004	0.002	0.001	0.1	0.02	0.004	0.002	0.001
	4*	1	-	-	-	4	1	-	-	-	4	-	-	-	-
3	4	1	-	-	-	4	1	-	-	-	4	-	-	-	-
4	4	-	-	-	-	3	1	-	-	-	2	-	-	-	-
5	4	4	-	-	-	4	1	-	-	-	4	-	-	-	-
6	4	1	-	-	-	4	2	-	-	-	2	-	-	-	-
9	4	4	-	-	-	4	1	-	-	-	4	-	-	-	-
13	4	4	-	-	-	4	4	-	-	-	2	-	-	-	-
16	4	4	-	-	-	4	4	-	-	-	4	-	-	-	-
17	4	4	-	-	-	4	4	1	-	-	4	-	-	-	-
24	4	4	4	1	-	4	4	-	-	-	4	-	-	-	-
26	4	4	2	-	-	4	4	-	-	-	4	-	-	-	-
27	4	4	-	-	-	3	2	-	-	-	3	-	-	-	-
28	4	4	-	-	-	4	4	-	-	-	4	-	-	-	-
29	4	4	4	1	-	4	4	-	-	-	4	-	-	-	-
30	4	1	-	-	-	4	1	-	-	-	3	-	-	-	-
31	4	4	-	-	-	4	3	-	-	-	4	-	-	-	-
43	4	4	-	-	-	4	3	-	-	-	4	-	-	-	-
46	4	3	-	-	-	4	-	-	-	-	3	-	-	-	-
48	4	3	2	-	-	4	3	1	-	-	3	2	1	-	-

\* 4 = ++++; 3 = +++; 2 = ++; 1 = +; - = negative.  
\*\* Complement 1:30; \*\*\* Complement 1:15; \*\*\*\* Complement 1:10.



This is shown in Table VII in the reactions observed with four syphilitic sera. The antigen of cholesterolized and lecithinized alcoholic extract of beef heart was titrated in an antish sheep system with 1:10, 1:20 and 1:30 dilutions of the same complement, at the same time and with the technic of the new test. In conducting the tests with the four sera the antigen was used in dose of ten units according to the results with the three different dilutions of complement and yet the reactions were not identical being more sensitive with 1:30 complement than with 1:20 and 1:20 more than with 1:10.

Similar results were observed with an antiox system (Table VIII) using the same dilutions of complement.

The same results were also observed with an antihuman system (Table IX) employing complement 1:1½, 1:5 and 1:10.

*These results indicate therefore the advisability of using as powerful hemolysis as possible in order to permit the use of smaller amounts of complement to avoid introducing into the hemolytic system such amounts of indifferent serum proteins in guinea pig serum complement or rabbit serum hemolysin as will interfere with the degree of complement fixation by syphilis antibody and lipoidal antigen.*

When tests with syphilis sera are conducted with antish sheep and antiox hemolytic systems employing the same antigen and 1:30 complement according to the technic of the new test, the results are almost identical (Table X). Insofar as the qualitative test is concerned employing 0.1 c.c. of patients' sera, the results are identical but in the quantitative tests minor differences may occur in the higher dilutions of serum.

*When tests are conducted with 1:30 complement in an antish sheep system, 1:15 complement in an antiox system and with 1:5 or 1:10 complement in an antihuman or antichicken system the qualitative reactions are usually identical or almost so, but the quantitative reactions are different in that the antish sheep system yields more sensitive reactions, that is, positive reactions with smaller amounts of syphilitic serum. These facts are shown in Tables X and XI by the results of a few comparative tests of this kind taken from a large series.*

*For these reasons the antish sheep system was adopted for the new test; the antiox system is just as good if 1:30 complement can be used. The antihuman and antichicken systems are just as satisfactory in a qualitative test but inferior for the quantitative test.*

## SUMMARY

1. The new complement-fixation test for syphilis based upon the results of studies in the standardization of technic may be employed with an antishoop, antiox, antihuman or antichicken hemolytic system.

2. With the new *qualitative* technic the results of tests with syphilitic sera and these four hemolytic systems are almost identical.

3. With the new *quantitative* test however, the results are not identical, the reactions being slightly more sensitive with the antishoop and antiox systems than with the antihuman and antichicken systems.

4. The differences in sensitiveness of the reactions with the different hemolytic systems are due to varying dilutions of complement employed. The tests with the antishoop and antiox systems are conducted with 1:30 complement and are more delicate than tests conducted with 1:5 and 1:10 complement in the antihuman and antichicken systems.

5. The lower dilutions of complement required in the antihuman and antichicken systems are due to the hemolysins which cannot be prepared as powerful as antishoop and antiox hemolysins.

6. The larger amounts of guinea pig serum complement and rabbit serum hemolysin required for the antihuman and antichicken hemolytic systems introduce sufficient serum proteins to reduce the degree of complement fixation by syphilis antibody and lipoidal antigen.

7. For conducting the new complement-fixation test with an antishoop system the hemolysin should be at least sufficiently powerful to yield a unit of 0.5 c.c. of 1:2000 with 0.3 c.c. of 1:30 complement. In an antiox system the hemolysin should at least yield a unit of 0.5 c.c. of 1:200 with 0.3 c.c. of 1:30 complement. In an antichicken and antihuman system the hemolysins should at least yield units of 0.5 c.c. of 1:40 with 0.3 c.c. of 1:10 complement.

8. The antigenic and anticomplementary activities of antigen are influenced by the dilution of complement employed in the titrations; for this reason the antigen must be titrated with 1:30 dilution of complement in the antishoop and antiox hemolytic systems and with 1:5 or 10 dilution of complement (preferably 1:10) in the antihuman and antichicken hemolytic systems.

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# STUDIES IN THE STANDARDIZATION OF THE WASSERMANN REACTION, XXXII\*

## A COMPARATIVE STUDY OF THE NEW COMPLEMENT-FIXATION TEST FOR SYPHILIS WITH OTHER METHODS

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(Received for publication, March 12, 1921.)

FOR the purpose of determining the sensitiveness and reliability of the new complement-fixation test for syphilis,<sup>1</sup> it has been tried out with *nine other methods* in the examination of selected sera from syphilitic and nonsyphilitic persons.

Six of these methods are based upon the use of unheated or raw serum. As previously stated these raw serum tests are usually more sensitive than tests employing heated serum,<sup>2, 3</sup> but are subject to certain disadvantages according to the technic employed, which have been previously studied and discussed.<sup>4</sup>

*One of the purposes of my new test was to build up a method possessing the very high degree of sensitiveness of raw serum tests without the disadvantages;* the object of this communication is to give the results of comparative tests showing how the new test has been found to compare with other well-known methods in these respects.

### METHODS EMPLOYED

The following methods were selected for this study because each is based upon a more or less distinctive principle; a description of the technic of each is omitted here for the sake of brevity, but we have very carefully followed the directions given in the articles referred to in the bibliography.

#### (A) *Methods Employing Unheated Serum:*

1. Noguchi test with guinea pig complement, antihuman system and an antigen of acetone insoluble lipoids.<sup>5</sup>

2. Seelman test with natural complement and hemolysin, guinea

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\*Investigation aided by funds accruing from the preparation of arsphenamine.  
I am indebted to Miss M. E. Trist, Miss Anna M. Rule and Miss Elizabeth Yagle for assistance in this work.

pig complement and antish sheep hemolysin being used as necessary and an antigen of acetone insoluble lipoids.<sup>6</sup>

3. Thompson test with native human complement, antihuman system and an antigen of acetone insoluble lipoids.<sup>7</sup> This technic was modified by using each serum undiluted and using two units of hemolysin instead of two units of serum (complement).<sup>8</sup>

4. Bartlett and O'Shansky test with natural human complement, natural antish sheep hemolysin and an antigen of acetone insoluble lipoids.<sup>9</sup>

5. Hecht-Gradwohl test with natural human complement, natural antish sheep hemolysin and an antigen of acetone insoluble lipoids.<sup>10</sup>

(B) *Methods employing heated serum and guinea pig complement:*

6. U. S. Army test of Vedder and Craig employing an antihuman hemolytic system and cholesterolized alcoholic extract of heart muscle as antigen.<sup>11, 12</sup>

7. Thomas and Ivy test employing an antish sheep hemolytic system and an alcoholic extract of syphilitic liver as antigen.<sup>13</sup>

8. New York City Department of Health test employing an antish sheep hemolytic system and an alcoholic extract of guinea pig heart as antigen.<sup>14</sup>

9. To these was added my former method<sup>15</sup> which employs an antish sheep hemolytic system and three antigens namely, cholesterolized alcoholic extract of beef heart, alcoholic extract of syphilitic liver and acetone insoluble lipoids. This method has been in use for over eight years and naturally was the one with which I was most familiar and upon the results of which I had learned to place a high degree of confidence. During the past year, all sera were tested routinely with this and the new method.

All the antigens were carefully titrated for each method; several authors of the above mentioned tests kindly furnished sufficient amounts of their own antigen which added to the accuracy and fairness of the comparative tests.

#### SERA TESTED

No effort was made to test a large number of sera but rather to work with a relatively small number carefully selected in order to exclude the sera of those individuals concerning whom there were differences in clinical opinion. Since the sera of *untreated* cases of secondary and active tertiary syphilis are apt to yield positive reac-

TABLE  
COMPARATIVE TESTS WITH SERA OF 25 SYPHILITIC INDIVIDUALS UNDERGOING TREATMENT

CASE NO.	HISTORY	INTRAVENOUS INJECTIONS	NOGUCHI TEST	THOMPSON TEST	BARTLETT & O'SHAUNESKY TEST	HECHT GRADWOHL TEST**	U. S. ARMY TEST	THOMAS AND IVY TEST	N. Y. DEPT. HEALTH TEST	AUTHOR'S FORMER TEST*	NEW TEST			
											0.1	0.02	0.004	0.002
1	Neuro-Syph.	35 arsphen.	Pos.	2***	1	1	1	1	—	1	2	—	—	—
2	Tertiary Syph.	27 arsphen.	—	—	—	—	—	—	—	—	1	—	—	—
3	Secondary Syph.	10 neoarsphen.	Pos.	4	4	4	4	4	3	4	3	1	2	—
4	Tertiary Syph.	25 neoarsphen.	Pos.	4	4	4	4	1	—	—	4	4	4	—
6	Neuro-Syph.	16 neoarsphen.	Pos.	4	4	4	4	2	4	4	4	4	—	—
7	Tertiary Syph.	24 arsphen.	Pos.	4	1	3	4	3	4	2	4	4	—	—
8	Secondary Syph.	16 neoarsphen.	Pos.	4	4	4	4	2	—	—	4	4	1	—
9	Tertiary Syph.	32 neoarsphen.	Pos.	1	2	1	—	—	—	—	2	—	—	—
10	Tertiary Syph.	7 arsphen.	—	3	1	4	3	—	—	3	3	1	—	—
11	Tertiary Syph.	22 arsphen.	Pos.	4	4	4	4	3	4	4	4	4	1	—
13	Tertiary Syph.	1 neoarsphen.	Pos.	4	4	4	4	4	4	4	4	4	4	—
14	Tertiary Syph.	2 neoarsphen.	Pos.	4	4	4	4	3	4	4	4	4	—	—
15	Secondary Syph.	13 neoarsphen.	—	—	—	—	—	—	—	—	—	—	—	—
16	Secondary Syph.	8 arsphen.	Pos.	4	4	4	4	1	4	4	4	2	—	—
17	Tertiary Syph.	1 neoarsphen.	Pos.	3	4	4	4	3	4	4	4	4	1	—
18	Tertiary Syph.	16 neoarsphen.	—	—	—	—	—	—	—	—	—	—	—	—
19	Neuro-Syph.	22 neoarsphen.	Pos.	3	4	4	2	—	4	4	3	1	—	—
20	Tertiary Syph.	6 neoarsphen.	Pos.	4	4	4	4	—	4	4	4	4	1	—
21	Tertiary Syph.	9 arsphen.	Pos.	4	4	4	4	4	4	4	4	4	1	—
22	Tertiary Syph.	8 neoarsphen.	Pos.	2	4	4	2	—	3	4	2	—	—	—
23	Secondary Syph.	31 neoarsphen.	Pos.	1	4	4	1	—	4	4	4	4	1	—
24	Tertiary Syph.	7 arsphen.	Pos.	4	4	4	2	4	4	4	4	4	—	—
25	Tertiary Syph.	19 neoarsphen.	Pos.	2	4	4	2	1	4	4	4	1	—	—
26	Tertiary Syph.	17 neoarsphen.	Pos.	4	4	4	2	3	4	4	4	2	—	—
27	Tertiary Syph.	No treatment	Pos.	2	4	4	2	—	4	4	4	4	1	—
5	Control	No treatment	—	—	—	—	—	—	—	—	—	—	—	—
12	Control	Percentage positive reactions with syphilitic sera.....	—	88	88	84	84	60	64	80	92	—	—	—

\* Results with tests conducted with an extract of acetone insoluble lipoids.

\*\* Results with the 0.2 c.c. dose of antigen.

\*\*\* 4 = + + + +; 3 = + + +; 2 = + +; 1 = +; — = negative.

tions with practically any complement-fixation test, they were not included in this study which had for its primary object a comparative study of the sensitiveness of the different methods.

#### RESULTS

The results observed with the sera of twenty-seven individuals, twenty-five of whom were cases of syphilis under treatment with arsphenamine and neoarsphenamine in the clinic of Dr. Jay F. Schamberg, are shown in Table I.

This table shows the strength or degree of complement-fixation with the nine control methods insofar as this is possible in qualitative tests. The strength of the Noguchi tests according to the +++, ++ method could not be given because many of the serum controls contained a few agglutinated erythrocytes which naturally reduced the accuracy of readings in the front or antigen tubes.

As shown in this table the raw serum methods gave 84-88 per cent positive reactions and the new test 92 per cent with 0.1 c.c. amounts of serum. With the exception of the Army method, the heated serum tests gave a few more negative reactions. I am quite sure that the use of cholesterolized antigen in the Thomas and Ivy and New York Department of Health tests would have yielded a few more correctly positive reactions than observed.

Table II is a summary of the reactions observed with these methods in tests conducted with a second series of sera from seventy-two syphilitic individuals under treatment; eight sera from nonsyphilitic controls yielded negative reactions with all methods.

In this series five raw serum tests yielded 74 to 83 per cent positive reactions while the new test yielded 86 per cent; of the heated serum tests the Army method yielded 78 per cent positive reactions and the other tests from 60 to 80 per cent, the differences being largely due in my opinion, to the antigens (Thomas and Ivy and N. Y. Department Health tests conducted with plain extracts).

Table III presents a summary of comparative tests with my former method employing three antigens, the new test and the Hecht-Gradwohl test; the majority of these sera were from individuals known to have syphilis and under treatment in Dr. Schamberg's clinic.

As shown in this table the new test gave at least 8 per cent more positive reactions than shown by the former test and at least 6 per cent more positives than a well-known raw serum test.

TABLE II  
PERCENTAGE OF POSITIVE REACTIONS WITH THE SERA OF 72 SYPHILITIC INDIVIDUALS, THE MAJORITY OF WHOM WERE UNDER TREATMENT

Noguchi Test	Thompson Test	Bartlett and O'Shansky Test	Hecht-Gradwohl Test	Seelman Test	U. S Army Test	Thomas and Ivy Test	N. Y. Dept. Health Test	Former Test* 80%	New Test**
74%	82%	83%	80%	78%	78%	60%	60%	63%	86%

\*80 per cent of positive reactions with antigen of cholesterolized alcoholic extract of heart; 63 per cent positive reactions with acetone insoluble lipoids.

\*\*Results according to the 0.1 c.c. dose of each serum.



TABLE III

PERCENTAGE OF POSITIVE REACTIONS WITH THE SERA OF 835 INDIVIDUALS THE MAJORITY OF WHOM WERE SYPHILITICS UNDER TREATMENT

Author's former Method			New Test**	Hecht-Gradwohl Test***
C. B. H.*	C. L.	A		
56%	58%	45%	66%	60%

\*C. B. H.—cholesterolized alcoholic extract beef heart; C. L.—cholesterolized and lecithinized alcoholic extract of beef heart; A—acetone insoluble lipoids of beef heart.

\*\*Results with the 0.1 c.c. dose of each serum.

\*\*\*Percentage of positive reactions with 755 sera; with 80 sera or about 10 per cent hemolytic indices could not be obtained owing to absence of hemolysin, complement or both.

*These results (shown in Tables I, II and III) apparently warrant the statement that the new test possesses as much sensitiveness as raw serum tests and considerably more than heated serum tests for syphilis antibody in the sera of syphilitic individuals under treatment.* Of course this involves the question of the significance of a positive reaction with the serum of a syphilitic individual during treatment with arsphenamines but at the present time I believe the use of these sera a good means for testing the comparative sensitiveness of different complement-fixation tests for syphilis antibody.

The summary in Table III also includes a large number of persons of whom there were no reasons for suspecting syphilis historically or clinically; all of these yielded negative reactions with the new test.

The sera and spinal fluids of a number of individuals included in Table III gave a positive reaction in the new test and negative reactions with one or both of the control tests. The histories of these individuals and clinical evidence have indicated that the positive reactions with the new test were apparently correct.

My primary object, however, was to submit the new technic to comparative tests with other methods using the sera of unquestioned cases of syphilis and depending upon specific treatment to so reduce the amount of antibody in the sera to bring out differences in sensitiveness of the various methods. Also to test the sera of persons in whom syphilis could be excluded with a reasonable degree of accuracy. I believe the results warrant three conclusions as follows:

## CONCLUSIONS

1. The new complement-fixation test for syphilis has proved equal or superior to raw serum tests in sensitiveness for the detection of syphilis antibody in the sera of syphilitic individuals under treatment and in clinically obscure cases of untreated syphilis.
2. The new test has not yielded any falsely positive reactions.
3. The new test is considerably more delicate than other heated serum tests for the detection of syphilis antibody in sera and spinal fluids.

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## FIBROID SUBCUTANEOUS SYPHILOMATA

### REPORT OF A CASE ASSOCIATED WITH SYPHILITIC BURSTITIS AND A REVIEW OF THE LITERATURE

BY HERMAN GOODMAN, B.S., M.D., NEW YORK CITY

(Received for publication, March 3, 1922)

**A**LTHOUGH no published reference to subcutaneous fibroid syphilomata could be found at the time of publication of our first paper on this rare manifestation of syphilis<sup>1</sup> a number of papers have since appeared in addition to our own added case, and reference to some unpublished cases has been made. It seems that the appearance of a third personal case presenting some rather unusual characters serves as an impetus for a review of the entire matter.

#### CASE REPORT

A. B., age thirty-eight, a native of Russia, presented himself at the Syphilis Clinic at Bellevue Hospital, Service of Dr. Mihran B. Parounagian (whose permission to publish this case report is gratefully acknowledged) complaining of pain in the left arm. He gave a history of having had a chancre in the coronary sulcus about 13 months previously, for which he had had only local treatment. On examination, the patient presented swellings at each olecranon prominence which were distinctly doughy in consistency and about the size of small hen's eggs. Within each of these swellings could be felt a movable small solid mass of irregular shape, which was apparently inside the bursa sac, yet not attached to any solid structure such as the bone or tendon. These swellings were considered bursa containing nodules of unknown nature. In addition, the patient presented symmetrically placed nodules about one inch and a half further down the forearm. The nodules were beneath the skin, about the size of a small bean, movable under the skin, and with the skin movable over the nodules. The nodule on the right forearm was somewhat larger than the one on the left. There was one more much smaller mass to be felt to the outside of the tumor of the right forearm, but there was no mass symmetrically arranged with this one. On the joint surface of the first interphalangeal joints of the third and fifth fingers of the right hand, and over the middle finger of the left hand were small reddened masses about the size of split peas. The only other mass on the patient was a soft one on the left leg a little below the knee on its mesial surface which was probably a dilated vein.

The patient said that the hard masses had been present about eight months.

The one on the left elbow (olecranon bursa) had been the first, and that the order of the others was: right elbow (olecranon bursa) below right elbow; below left elbow; left hand; and right hand. The most recent nodule was of three months' duration only. The nodules themselves gave no pain, but he did experience pain in the arm. Further examination disclosed no evidence of cutaneous syphilis.

The Wassermann taken on the day of admission was reported three-plus positive. One of the nodules was removed and found to consist macroscopically of three small definitely hard masses, each no larger than the head of a fancy pin, enmeshed in the subcutaneous tissue. No connection with bone or tendon could be made out at the time of the biopsy. The small nodule cut with a "hard" feel. The tissue was prepared and sectioned. Dr. Douglas Symmers, Director of the Laboratories at Bellevue Hospital reports as follows: "Microscopic examination shows a matrix of poorly nucleated and poorly fibrillated fibrous tissue which in places is opaque, glassy and hyalinized, in other places necrotic. Scattered through it are numbers of small blood vessels, practically every one of which is surrounded by a broad zone of round cells of the lymphocytic or plasma cell variety. Some of the vessels are filled with red blood cells, but the majority show marked proliferation of the endothelial lining, so much so that in some instances the lumen is occluded. The vessel walls themselves are thickened. Microscopically the lesion is best interpreted as syphilitic."

An x-ray examination of both forearms showed no abnormality of the bones. There was infiltration of the soft tissue in the region of both retroolecranon bursas. An exostosis springs from the posterior border of the olecranon. The prints from the x-rays are given.

The points of special importance in this case are the early appearance of the nodules, and the presence of bursitis and subcutaneous nodules in one patient. In order to make the matter of the subcutaneous nodules a little clearer it might be well to review the few cases known.

#### REVIEW OF LITERATURE

As mentioned in the introduction, the first case of subcutaneous nodules in a syphilitic known to be reported was that of Goodman and Young.<sup>1</sup> The patient, R. R., was an American woman, aged 29 years, and of more than average intelligence. She had married at 18 years. She had one abortion at four months, and did not become pregnant again. Her husband, who had always been well, died in a railroad accident after two years of matrimony. At 22, she had married again. Although her husband is healthy and they desire children she has not become pregnant. The presence of the tumors on the extremities had been noted for about eight years. The first lesion was on the extensor surface of the elbow, and about the size of a pea. Additional masses have appeared since in an unnoted order. For instance, the mass on the



Fig. 1.—Fibroid subcutaneous syphilomata associated with syphilitic bursitis. Right elbow.



Fig. 2.—Fibroid subcutaneous syphilomata associated with syphilitic bursitis. Left elbow.



Fig. 3.—Fibroid subcutaneous syphilomata associated with syphilitic bursitis. Location of the lesions.





Fig. 4.



Fig. 5.

Figs. 4 and 5.—Fibroid subcutaneous syphilomata associated with syphilitic bursitis; right and left hands showing lesions over joints.



Fig. 6.



Fig. 7.

Figs. 6 and 7.—Fibroid subcutaneous syphilomata associated with syphilitic bursitis. X-ray side views of right and left forearms.





knee was of appreciable size when first noted four years before. The nodules in the left elbow extended in a line from the olecranon process to the styloid process of the ulna. It was semiglobular, and about 3 by 2 cm. It was entirely under the skin, which was freely movable over it. The tumor appeared attached to or part of some subcutaneous structure. To the touch the mass felt lobulated, and made up of individual although connected masses. (This seems more or less important in view of the findings in the newly reported case that on biopsy the mass seemed made up of three smaller masses.) The masses were distinctly hard and could not be indented by pressure over them. The skin over the lesion was not stretched, nor was it red. The second tumor on the left arm was about  $2\frac{1}{2}$  cm. distant from the first. It was 3 by 4 cm. It appeared made up of only two connected lobules rather than many, and otherwise was of the same character as those of the left arm. Over the left knee and occupying the space of the normal indentation between the patella and the tubercle of the tibia was a single mass about 2 by 2 cm. which gave the same resistance and was of the same structure as that described for the elbow tumor. The mass moved with the motion of the leg on the thigh and gave no discomfort. The Wassermann reaction was reported positive to both the alcoholic and cholesterine antigens. Part of one of the nodules, removed for section, was stained with Levaditi silver impregnation method but no spirochetes were found. The microscopical diagnosis of the tissue was "Granuloma—probably syphilitic." This patient was not given the therapeutic test as both Young and myself were called into active service (latter part of 1917) and attempts made since my return to reach the woman have been unsuccessful.

The second patient observed and reported<sup>2</sup> was an American, aged 36, and well educated. He had married at 21, and had one child. At 26, the patient acquired a lesion of the penis by extramarital intercourse. No symptoms of generalized syphilis had ever been noted. The presence of tumors on the left arm had been noticed about 8 years. Additional masses have appeared since in an irregular order. Many physicians had been consulted regarding these tumors, but no definite diagnosis had ever been made. The tumors gave no subjective symptoms, but if a lesion were contused, the patient felt pain, and would be troubled for a variable

time according to the force of the blow. The lesion on the dorsum of the right hand was first noticed about six months ago. On examination, the patient presented two tumors on the right forearm below the olecranon. The first was about 2 in. below the olecranon, about an inch in diameter, and raised above the surface for about  $\frac{1}{2}$  inch. It seemed formed of one mass. It was movable under the skin and was movable over the underlying structures for a limited extent. The second mass was slightly smaller than the first, and situated about 1 in. from it. It was also raised, but not so much as the first mass. The left forearm presented three tumors about the elbow. The largest was situated symmetrically with the larger of the two on the right forearm, but was even a little larger than that one. The second lesion on the left forearm was over the inner condyle. It was about  $\frac{1}{2}$  in. in diameter, and about the same height above the skin. A third tumor on this arm was about 2 in. from the olecranon and was about  $\frac{1}{2}$  in. in diameter and only slightly raised. On the left leg, almost over the tubercle of the tibia was a single tumor smaller in size than any of those on the arms. The lesion gave the patient more trouble than the others because it was subject to trauma. The skin over the tumor was perfectly normal. The lesion on the dorsum of the hand was a serpiginous gumma. The Wassermann was performed in duplicate and reported four-plus positive from both laboratories. (The blood of the wife was also four-plus positive.) Following the venipuncture for the serologic test a small hemispherical mass about  $\frac{1}{4}$  in. in diameter appeared at the site of the puncture. In rapid order similar masses to the number of at least eight appeared along the forearm from which the blood had been taken. These small masses gave no subjective symptoms. (The masses were very similar in appearance to those which the newly reported patient presented over the interphalangeal joints.) One of the masses from about the elbow was removed and sectioned. The report showed a "fibrous tissue with heterogenous arrangement, fairly vascular, with round cells scattered through the tissue, and aggregated near one area of necrosis. (Part of the necrotic area had been lost in imbedding.) There were a large number of plasma cells amongst the round cells and scattered polynuclears. The arteries showed a marked thickening." The similarity of this report with that of our new case is indeed striking, although it should be



Fig. 8.



Fig. 9.

Figs. 8 and 9.—Fibroid subcutaneous syphilomata associated with syphilitic bursitis. Anterior-posterior x-ray views of right and left elbows.



Fig. 10.—Subcutaneous syphilomata. Female case of Goodman and Young.



Fig. 11.—Subcutaneous syphilomata. Male case of Goodman.



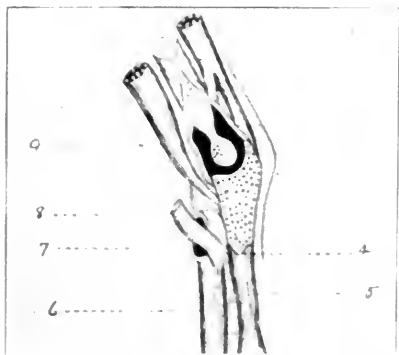


Fig. 12.—Bursae about elbow (after Delbierre from Churchman). 1, triceps; 2, humerus; 3, joint cavity; 4, bursa cubitalis interossea is frequently found at this site; 5, ulna; 6, radius; 7, bursa bicipitoradialis; 8, biceps; 9, brachialis anticus.

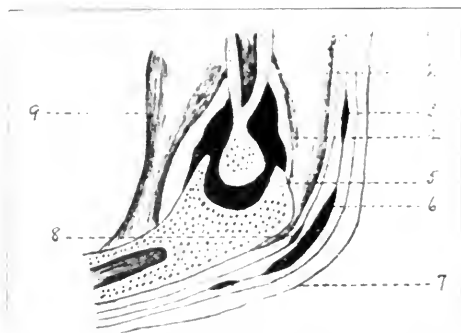


Fig. 13. Bursae about the elbow (after Delbierre from Churchman). 1, humerus; 2, triceps; 3, supra-olecranon bursa; 4, joint cavity; 5, ulna; 6, subcutaneous retroolecranon bursa; 7, intraolecranon bursa; 8, subaponeurotic retroolecranon bursa; 9, brachialis anticus.



Fig. 14.—Subcutaneous syphilomata in female case of Goodman and Young. Symmetry of lesions and similarity to other cases.



noted that the necrosis of which there was no clinical indication in this patient, was not so marked histologically. Treatment with neoarsphenamine gave immediate improvement in the cutaneous gumma of the dorsum of the hand, and diminution of the tumor masses. These disappeared in order from the smallest, that on the leg, to the largest, that on the left forearm. The small hemispherical masses, which were mentioned as appearing after the venipuncture, disappeared without leaving a trace. The other less recent tumors have left a sense of induration.

Between the time of publication of my first two cases of this rare manifestation of syphilis, Weber<sup>3</sup> described a similar case. His patient was a man, aged sixty years, who gave no history of syphilis, but whose blood was strongly positive to the Wassermann reaction. The patient had multiple subcutaneous rather hard nodules on his lower extremities (chiefly on the right lower extremity) painless, and hardly tender on pressure, varying from the size of a hazel nut to that of a medium sized chestnut, and all of them situated between the ankle and a level just above the knee except one which was on the outer side of the middle of the right thigh. They began to appear about 8 years before, but were according to the patient, at first temporarily removed by some kind of medicine. For biopsy purposes, one of the nodules was removed. It seemed macroscopically to consist of a hard fibrous mass irregular in outline (not encapsulated). Microscopic examination showed a dense mass of fibrous (scar-like) tissue surrounded by and including numerous foci of chronic inflammatory small cell infiltration (lymphocytes, fibroblasts, and some plasma cells). No hemorrhage and no necrotic areas were seen in the section, nor was there any decided obliterating thickening seen in the small vessels. This examination proved that the nodules were due to some chronic inflammatory disease, probably syphilis.

More recently, Fox<sup>4</sup> reported a case of this manifestation of syphilis which I had had the pleasure of seeing. The patient was a negress (about three-fourths pure blood) aged forty-five, who was an undoubted syphilitic presenting a nodular syphiloderm of the left forearm, and a four-plus positive Wassermann reaction. The nodules were present on both forearms, along the ulna border, were solid, cartilaginous, hard, but painless. The overlying skin was normal in appearance and freely movable over the nodules

the latter being only partly movable on the deeper parts. There was one nodular mass, elevated one-quarter of an inch on the ulna side of the olecranon while other small nodular masses were situated upon both borders, about 2 inches from the olecranon. In the region between the patellas and tuberosities of the tibiae, there were semiglobular elevated masses having characteristics similar to the lesions on the forearms, except that they were slightly less firm to the touch. The nodule on the left knee was about the size of a horse chestnut and somewhat larger, harder and more distinctly globular and movable than upon the right knee. X-ray examination failed to show any abnormal bone changes. Histologic diagnosis by Dr. J. Highman was "organizing gumma." Antisyphilitic treatment had reduced the nodules to one-fifth their former size. The duration of the lesions had been two years for the elbows, and about a month later for the knees.

Fox mentions a second case under his observation in which the patient, a negress, aged thirty-four, showed lesions which were both subcutaneous and cutaneous. The former were irregular, extremely hard masses to which the skin was attached in places and movable in others. They were all freely movable on the upper parts. The individual masses were about the size of walnuts. In the skin were a few dull bluish red pea-size elevated nodules, hard, painless, and covered by smooth unbroken skin. There were similar nodules on both knees immediately below the patellae. They were, however, considerably smaller in size than on the forearms. The Wassermann reaction was four-plus positive. The lesions were said to have appeared about thirteen years previously and to have reached their maximum development in two years.

Although at the meeting of the Section of Dermatology of the Royal Society of Medicine before which Weber presented his case, no one present had seen or heard of a similar case of the development of organized fibrous nodules, Weber reported that visceral syphilis might become fibrotic. Some of the Members of the American Dermatological Society before which Fox read his paper, however, were able to add several cases in their own experience. Fordyce had photographs of a case with the nodules situated on one elbow and sharply circumscribed. Lane had had a patient of about forty-five with a hard subcutaneous nodule about the size



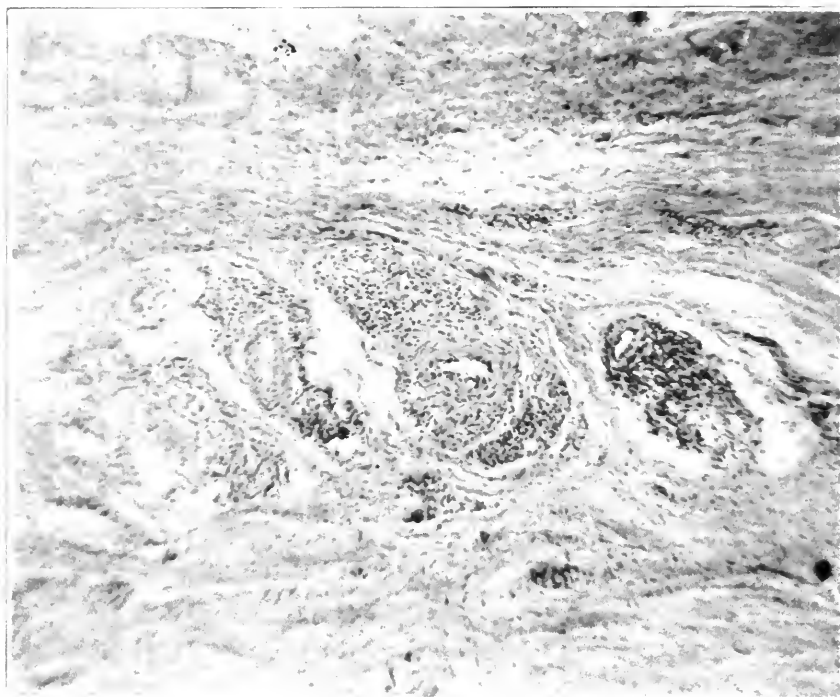


Fig. 17.—Siphomatous syphilitic arteriole (arteriole) from mass of fibroid tissue, Young, L. O. (Am. J. Ophth., 1922, 17, 147).

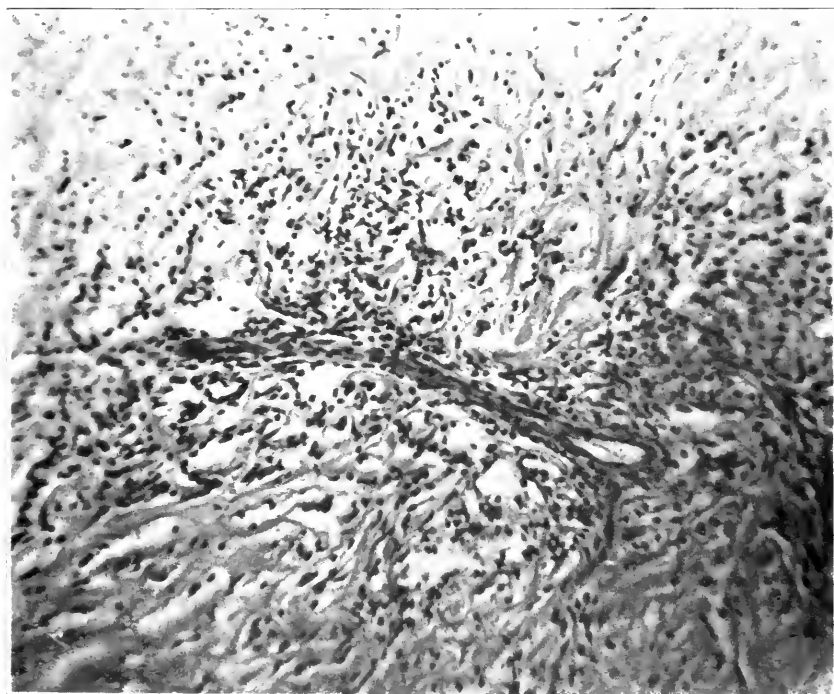


Fig. 18.—Siphomatous syphilitic arteriole (arteriole) from mass of fibroid tissue, Young, H. C. (Am. J. Ophth., 1922, 17, 147).



of a hickory nut a little below each elbow, and a nodular syphiloderm over the right elbow. The nodules were almost gone, although still palpable, after six injections of arsphenamine. Highman mentioned a case of gumma of the hand, over the tendons but not connected with them, which developed rather rapidly and disappeared under antisyphilitic treatment. (I had had the opportunity of studying the patient at The New York Skin and Cancer Hospital, and the lesions were not of the character of those about the elbow or knee joints of the type now under discussion. Highman's case was one probably of an even rarer variety.) Schamberg said that he had had the opportunity of seeing two cases, both in colored women, who presented extensive lesions on the arms and below the elbows, the skin being free and movable over these growths that were of cartilaginous nature. He brought up the question whether this condition was not more liable to occur in the negro race by reason of their well-known tendency to develop overgrowth of fibrous tissue.

#### JUXTAARTICULAR NODULES

Stimulated by a tropical residence of two years at the time of the first case report, I included a lengthy discussion of the comparison of the subcutaneous fibrous nodules with the juxtaarticular nodules described by Jeanselme.<sup>5</sup> Clinically the juxtaarticular nodules are of various sizes, globular or polyglobular, most often collected in masses. In the beginning the tumors lie deep in the subcutaneous tissue. Some of them are movable and roll under the fingers like ganglion; others appear adherent to periosteum, from which they possibly spring. Later, these nodules become more superficial and are incorporated in the skin. Later still they raise from the surface as protuberances of very hard consistency. The skin undergoes no modification; it is only distended and perhaps discolored at its highest point. The nodules are remarkably symmetrical. They occupy the external aspect of the extremities, surmounting by preference the bony prominences and grouping about the joints. Neither microscopic nor bacteriologic studies have revealed their true nature, but the generally ascribed cause for the nodules is the habit of the natives to lie with the elbows and knees in contact with the ground.

## SYPHILITIC BURSTITIS

Syphilis of the bursa formed the subject of a report by Churchman in 1909.<sup>6</sup> He had been able to collect about 28 cases, not all proved, of syphilitic bursitis. The bursae about the elbow lie in connection with the biceps and triceps muscles. Those at the posterior aspect of the elbow are of more importance in connection with syphilis than the well-known bicorporadial bursa. They lie on two planes (Delord); that is, between the superficial fascia and the aponeurosis of the triceps (subcutaneous retroolecranal bursa) or under this aponeurosis (subaponeurotic retroolecranal bursa). The superficial bursa lie behind, above, and below the olecranon, and may communicate with one another. I have made photographic copies of the cuts presented by Churchman of these parts.

The symmetry of the bursopathy, and the affection in the retroolecranal bursa are especially mentioned under the heading of diagnosis by Churchman—factors present in the case reported in this communication. The other masses presented by the patient which were distant from the bursae and along the forearm had no relation to bursae and were examples of the fibroid subcutaneous syphilomata, which have formed the basis of earlier communications. In this particular case, two rare manifestations of syphilis were coexistent.

## XANTHOMA TUBEROSUM MULTIPLEX

The localization of this type of tumor, at the elbows and knees is about the only point in which it simulates in any way the tumors of the syphilitic manifestation considered in this article.

## TREATMENT

Despite the fact that the lesions of subcutaneous fibroid syphilomata are distinctly hard, antisymphilitic treatment in the form of arsphenamine or neoarsphenamine quickly and entirely causes the disappearance of the tumors. Both cases which I had the opportunity to treat with these drugs responded satisfactorily. Fox's patient received but one injection of neoarsphenamine and six intramuscular injections of mercuric salicylate. The lesions on the knees had decreased to one-fifth of their original size, while those on the elbows had almost entirely disappeared. This treatment had been sufficient to promptly clear the nodular syphiloderm

which the patient also presented. Weber's patient showed no response to mixed treatment. The bursa lesions responded to the treatment in A.R.

## COMMENT

The newly reported case of fibroid subcutaneous syphilomata differs from the others reported in that they followed the first appearance of known syphilitic infection, the chancre, by a very short interval, and that the masses were of shortest duration. In addition, the patient presented a symmetrical syphilitic bursitis. This lesion of itself is rather uncommon. The apparent sites of predilection for these curious tumors are about the elbows and knees. Practically all the cases occur in these locations (Weber's case is the exception in this regard). The bursitis lesions also favor the elbows according to Churchman. Why this should be so remains unknown. Schamberg's suggestion regarding the condition favoring the colored race by reason of the well-known tendency of this race to develop overgrowth of fibrous tissue seemed important as both of his cases and two of Fox's were in the negro race. All the other patients were white. No doubt more of these cases have been seen than the few reported cases would indicate. Now that attention has been called to these syphilitic manifestations they should be more readily diagnosed, and it is hoped the further studies will clear up many of the unknown factors.

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## DIFFUSE SYPHILITIC MASTITIS

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(Received for publication, July 13, 1922.)

THE glandular tissue of the breast may be the site of gummata, presenting a distinct tumor with or without ulceration, or of diffuse syphilitic infiltration. Very little is said in the American literature concerning either one of these conditions. Localized gummata are rare but certainly diffuse infiltration of the breast due to syphilis is much less frequently encountered.

### LITERATURE

The earliest observer to mention syphilis of the breast was Astruc in 1736.<sup>1</sup> He evidently was impressed with the similarity of the tertiary syphilitic lesion to cancer of the breast as he speaks of "cancer of the breast as one of the symptoms of syphilis peculiar to women."

Sauvages<sup>2</sup> in 1768 recognized the likelihood of syphilis as an etiology factor in certain lesions of the breast when he mentions "Pox Cancer of the Mamma." He reports a case of a woman thirty years of age, with ulcerations in the vagina and mouth, who presented a hard and irregular tumor the size of an egg in each breast. All these manifestations disappeared under the administration of mercury. Bierchen<sup>3</sup> in 1775 noted that a tumor of the breast disappeared under iodine.

Thompson<sup>4</sup> in reviewing the literature on gumma of the breast states that neither Hunter, Bell, nor Swediaur, who were the foremost observers during the latter part of the eighteenth, and early part of the nineteenth centuries, make any reference to syphilis of the breast. However, he found that during the nineteenth century Richet, Yvaren, Verneuil, Velpeau, observed tumors of the breast which disappeared under mercurial treatment. Their descriptions, however, are of gummata only.

It is to Lancereaux<sup>5</sup> that credit is due for first drawing a line of distinction between gummata and diffuse syphilitic processes in the

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glandular tissue of the breast. In 1866 he observed a case of diffuse mastitis disappear under mercurial treatment and at the same time reported three cases of Ambrosoli's.<sup>6</sup> The German observers, Finger, Neumann, and Von Zeissl have made a similar distinction between gummata and diffuse lesions of the breast due to syphilis. Julien<sup>7</sup> more recently observed two cases of diffuse infiltration which occurred in men. He believes that men are more frequent sufferers than women from diffuse infiltration with sclerosis of the breast.

Burnier<sup>8</sup> has recently made a very complete search of the literature, and finds only thirty cases which he is willing to accept as diffuse syphilitic mastitis.

So few cases of syphilis of the breast have come to autopsy or operation that pathologist's descriptions are rare. However, Reinecke<sup>9</sup> in 1899 described that of luetic mastitis. The cut surface of the tissue presented yellowish red and red foci, of pin-head size elevated above the surface, which was firm and dry. The projections were due to proliferation of interlobular connective tissue which was replacing degenerated glandular epithelium. All the vessels were thickened.

The following report presents a case of diffuse infiltration of the whole breast.

#### AUTHOR'S CASE REPORT

Mrs. C., age forty, white, at present living with second husband. She has one son seventeen years of age. He shows no congenital stigmata and blood Wassermann is negative. *Past Medical History:* Fifteen years ago this patient had some ulcerations on the labia majora, but there was no history of a cutaneous eruption following them. She has never had persistent headaches or bone pains. Three years ago she had some ulcerations in the throat which were very troublesome, but disappeared after much swabbing and cauterization by her physician.

November 6, 1920, this patient was admitted to the Clinic for Syphilis of Ohio State University complaining of enlargement of the right breast and a tender lump in the axilla. She first noticed this enlargement about August 1919. As there was no pain or discomfort except from increased weight, she gave it little consideration until a hard tender nodule appeared in the right axilla. She consulted her physician in November, 1919, and he prescribed an ointment for her breast. She used it faithfully, but the breast and nodule in the axilla continued to enlarge. *Physical examination November 6, 1920.* White woman apparently fifty years of age, gray haired, fairly well nourished and intelligent. Scalp negative; eyes reacted to light and distance, throat and mouth clean.

The postcervical, inguinal and epitrochlear glands were enlarged. The skin showed no evidence of previous lesions.

The right breast was easily three times as large as the left and pendulous; its lower border was three inches lower than that of the left. Its appearance was that of a red and blue mottled, glistening mass hanging from the chest wall. It was symmetrical, smooth to touch, no nodules palpable. The nipple protruded normally, skin not adherent and the mass not adherent to the chest wall. It was of doughy consistency, but not edematous and no definite nodule or nodules could be palpated. On palpation the breast felt very much like a mass of cotton batting wadded under the skin, fat and superficial fascia. There was no palpable line of demarkation between the mass and the chest wall. Upon raising the right breast it seemed like lifting a heavy, dead weight. There were no painful areas, points of fluctuation, or increase in temperature of the mass. Palpation revealed the whole breast involved in the process. One gland about 2x2.5 cm. was palpable in the right axilla. It was not painful but tender to deep palpation. Knee reflexes were normal. No Romberg. Temperature per os, normal. Blood Wassermann 2-plus, Craig, November 6, 1920.

From November 18, 1920, to January 20, 1921, this patient received three grams of salvarsan and ten grains of mercuric salicylate by intramuscular injection. Treatment was suspended for one month, at which time, February 24, 1921, the Wassermann test was two-plus (Craig). After the second injection of salvarsan this breast began to resolve rapidly. One week after the first injection of salvarsan (arsenobenzol, Shamberg) 0.5 gm. there was no appreciable diminution in the size of the breast. A second similar injection of salvarsan was given. The patient returned in one week, this time, examination showed the breast to have decreased nearly a third in size, the skin had lost its glistening appearance and the axillary gland was no longer tender. We did not ascribe the breast condition to syphilis until this time, rather believing we had a diffuse mastitis of some other origin in a syphilitic individual. The diminution in size continued rapidly and symmetrically, and at the end of the sixth week had returned to normal size. At this time there were no nodules or tender areas palpable and the axillary gland was markedly reduced in size. A second course of treatment consisting of 3.5 gm. of salvarsan and twenty injections of mercuric salicylate was given. Another month's rest was allowed, at the end of which time the Wassermann was two-plus (Craig). This patient has been under constant observation and treatment and has persistently run a two-plus Wassermann.

#### DISCUSSION

Syphilitic mastitis may occur during any stage of the disease. Burnier found seventeen occurring during the early or late secondary stage, ten during the tertiary stage, and three in hereditary syphilis. Two-thirds of these cases were in women. The physiologic activity of the gland may account for the greater number occurring in women. However, the puerperium or trauma is not



recorded as an etiologic factor. The severity of the constitutional disease does not play any rôle in the occurrence of involvement of the breast in gumma or diffuse syphilitic processes. Burnier found nineteen cases out of twenty-nine unilateral.

There are two distinct forms of the disease found clinically: there may be a diffuse infiltration of one or more lobes of the gland which gradually extends into the surrounding normal tissue or the invasion may be evidenced by multiple nodules in the glandular tissue which are more or less definitely circumscribed. These may occur in one or more lobes varying greatly in size and shape and for the most part in the retroareolar region. Either one of the processes may present a mass of induration in the glandular substance with an increase in its size or the process may double or triple the size of the breast. Pain is usually absent but may be spontaneous or produced by pressure. Twelve out of thirty cases collected had spontaneous pain or sensitiveness in the breast. Pain was elicited on pressure in eleven. Four had spontaneous pain as well as pain on palpation. The axillary glands are usually unaffected but may give rise to pain on pressure. The diffuse un-circumscribed invasion more often gives rise to large indolent tumefactions.

There are two cases of massive, indolent tumefaction recorded. (1) Matzenauer's<sup>10</sup> patient was seventeen years of age; she presented herself two months after the chancre, with the right breast three times as large as the left. (2) Stimmel's<sup>11</sup> patient was a male, nineteen years of age, with an indurated infiltration which made the breast three times as large as normal. Both of these cases occurred in young adults and during early general invasion of the body with the spirochetæ.

The diagnosis of gummata or diffuse infiltration of the breast is not likely to be confused with cancerous and precancerous conditions of that gland. To eliminate a syphilitic process in the breast because the lesion is indolent, movable in glandular tissue, not attached to the skin, and because health is preserved will lead to many missed diagnoses of the condition.

One must not give too much weight to the diagnostic sign of adherence or nonadherence of the skin over the infiltration of the breast. Burnier's collection showed five cases out of thirty in which the infiltration was adherent to the skin. Burnier's own

case is very interesting in this connection. His patient, a woman 42 years of age, eight years after a chancre, presented a hard diffuse infiltration with ill-defined margins affecting many lobes of the breast. The tumor was the size of an orange, indolent, movable, but adherent to the skin which was normal in color but depressed at points in such a fashion that it presented the appearance of the outer surface of an orange peel. In the light of this case a retracted nipple should not exclude a diagnosis of syphilis. Gay<sup>12</sup> records a case in which the nipple was retracted, his patient being nineteen years of age.

The axillary glands were enlarged in four of the thirty cases collected by Burnier. My case adds a fifth in which the patient was more concerned about the enlarged gland than the weight or enlargement of the breast.

As is well known there is a close relation between trauma and the occurrence of the lesions of syphilis. The breast is subject to periodic physiologic traumata, as well as external traumata. In women, especially, acquired syphilis often runs a mild, insidious course. It would seem, therefore, that syphilis of the glandular tissue of the breast should be encountered more often. If those patients who presented themselves with breast lesions were carefully gone over for evidence of syphilis, and more frequently blood examination made, an occasional breast would be saved.

Diffuse syphilitic mastitis usually clears up under specific medications very rapidly, a few weeks showing a complete retrogression of the process, but it is evident from the cases reported that the classical symptoms and signs of syphilis of the breast may not be evident and the process may simulate cancer. The case of Lapowski<sup>13</sup> is classical in this respect. His patient had a tumor of the breast three years before, cured by mercurial treatment. At the time of second presentation, the infiltration was adherent to the skin at one point, there was glandular enlargement and the patient complained of pain. Pollitzer and Robinson and other authorities leaned toward the diagnosis of carcinoma in this case and advised amputation of the breast if cure was not effected in two months. It took six months to effect the disappearance of lesions. Rouanet<sup>14</sup> and Burnier<sup>15</sup> have also reported cases in which it took several months to cause the lesion to disappear.

While Lapowski's case presented three prominent symptoms of

cancer, viz., pain, adherence to the skin, and glandular enlargement, it emphasizes another point, that rapid retrogression of diffuse infiltrations due to syphilis is not always the rule and therein lies another stumbling block in the diagnostic path of breast conditions.

Abnormal involution of the breast may give rise to clinical picture that is impossible to distinguish from diffuse syphilitic mastitis. This is not surprising since a similar pathology is present in both conditions. The mass is firm and irregular with fibrous strands extending in many directions or it may be irregularly flattened. It is not, as a rule, adherent to the chest wall or the skin. Pain is usually absent but may be a prominent symptom. Sensitiveness in the breast may be a very early and persistent symptom. Retraction of the nipple may be present but is not a usual finding. Just so the axillary glands may or may not be enlarged in simple inflammatory hyperplasia. Abnormal involution is a process in which there is more or less generalized fibrosis and obliteration of the vessels with subsequent disappearance of the periductal tissue replaced by interlobular connective tissue. The syphilitic process is always characterized by fibrous tissue hyperplasia and rich lymphocytic perivascular infiltration. In the breast it is undoubtedly one of numerous granulomata distributed throughout the interstitial tissue, that never necrose but are replaced by fibrous tissue.

#### SUMMARY

A case is reported of massive indolent tumefaction of the whole breast, due to a diffuse involvement with a syphilitic process, in a white woman, forty years of age, fifteen years after the infection with the spirochetæ, three years after recurrence of secondary symptom in mouth and throat and a positive blood Wassermann test.

The right breast was at least three times as large as the left. It was not painful or sensitive, but gave rise to an enlarged, tender axillary gland on the right side.

Antiluetic treatment caused the breast lesion to disappear very rapidly and completely and it has remained cured for the past year. Treatment has as yet not produced a negative blood Wassermann. The history of syphilis, the nature of the lesion, and the

results of treatment justify the diagnosis of diffuse syphilitic mastitis.

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“A STUDY OF THE WASSERMANN REACTION IN A LARGE  
GROUP OF SUPPOSEDLY NONSYPHILITIC INDIVIDUALS  
INCLUDING GROUPS OF DIABETICS AND  
NEPHRITICS”

A Correction by the Author

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(Received for publication, September 22, 1922)

THE article under the above title which appeared in *The American Journal of Syphilis* for April, 1921, volume v, page 284, contained a misstatement with reference to the laboratories of the State Department of Health which the author sincerely regrets and desires to correct.

The error in question refers to a small group of diabetics suffering severely from undernutrition and exhibiting marked blood lipid changes, in whom Wassermann tests were obtained with wide and inconstant variations. In the article it states that these reactions were observed both in the laboratory of the Hahnemann Hospital as well as that of the State Department of Health and the reader is given the impression that they were in the nature of check tests which was untrue. A review of the data shows that the tests with the unusual variations were made in the Hahnemann Hospital while those performed in the State Laboratory were fairly uniform, consistent and essentially negative. It is further noted that the tests made in the hospital in which positive reactions occurred were on the bloods of patients extremely ill with diabetes and on low diets. When the diabetes and severe undernutrition were relieved, the blood Wassermanns became negative. The samples sent the State Laboratory were taken chiefly in this second stage. This phenomenon has been observed in a number of additional cases not reported. As stated in the original paper, whether or not these variations are due to faulty technic or physical chemical changes in the sera the author is unable to state.

When this study was undertaken the laboratory of the hospital was not operating under the approval of the State Department of

Health. The author, however, obtained from the Division of Laboratories a detailed statement of the Wassermann technic employed in the State Laboratory and submitted it to the director of the hospital laboratory. Assurance was received that the technic of both institutions was essentially similar. Several hundred tests reported in the study were made in each laboratory, a number of them being check tests which quite uniformly agreed.

The study was presented by the author who professes no special knowledge or skill in Wassermann technic, from a purely clinical point of view. The desirability of standardized technic and methods in hospital laboratory practice is clearly obvious. The important and original conclusions should again be emphasized, namely that a diagnosis should not be based solely upon a Wassermann report, but this report should be interpreted in the light of clinical observation in each case.

# THE SYPHILIS COMPLEMENT-FIXATION REACTION IN PREGNANCY WITH SPECIAL REFERENCE TO THE KOLMER REACTION\*

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(Received for publication, July 5, 1922.)

SINCE the advent of the Wassermann reaction for the diagnosis of syphilis its specificity has constantly been a subject of discussion and dispute. It is, of course, not a biologically specific reaction, for positive results are observed in frambesia just as well as in syphilis and the extracts employed as antigens are not specific, but at the present day it is generally admitted that a positive reaction with an acceptable technic indicates syphilis, though not necessarily syphilis in an active state.

A great deal has been written of late regarding pregnancy as one of the conditions in which bodily reactions are so altered that a falsely positive Wassermann reaction may result when syphilis is not present. This assertion is so often made that many obstetricians have begun to feel that they cannot trust the Wassermann reaction at all as an aid to the diagnosis of syphilis prenatally. As long ago as 1916 Falls and Moore<sup>1</sup> wrote that pregnancy increases the lipoidal content of the blood and that theoretically this should unbalance the Wassermann reaction. They report an apparently false reaction in a case of eclampsia. Menton<sup>2</sup> in 1918 reports fourteen positive reactions in a series of 357 tests in pregnant women all of which reacted negatively after delivery. In one of these cases there was a history of a previous syphilitic infection. In two others the cord blood was positive. Two others had premature, macerated babies and autopsy showed syphilitic lesions. Three had symptoms that suggested syphilis. The remaining six showed no abnormality except that the placentas contained nonsyphilitic lesions and none of them had any history of syphilis. Cornell and Stillians<sup>3</sup> also suggest the possibility of falsely positive Wassermann reactions in pregnancy. Haythorn<sup>4</sup>

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\*From the Pathological Laboratories of the Graduate School of Medicine of the University of Pennsylvania.

in a paper read before the Pennsylvania State Medical Society in 1921 reports "eight instances of four-plus reactions on the bloods of pregnant women, who presented no evidence of syphilis." The blood of one of these examined one month after delivery was negative. In the discussion following this paper Judson Daland of Philadelphia said, "One must always hold in abeyance any opinion as to the value of the Wassermann reaction when \* \* \* there is any marked alteration in metabolism, as for instance in \* \* \* pregnancies with lactosuria." Williams and Kolmer<sup>5</sup> examined the bloods of forty pregnant women and found that seven gave a positive Wassermann reaction, four of them, however, with cholesterolized antigens alone. They were of the opinion that all of these were true syphilitic reactions. They also say, "It is to be doubted if the reported positive Wassermann reactions in eclampsia are due to any changes in the blood as a result of the toxemia. It may be that some of the occasional moderately high blood pressures met with in pregnant women who are evidently not toxemic, are the result of a syphilitic endarteritis." Kolmer<sup>6</sup> of Philadelphia and Lisser<sup>7</sup> of San Francisco believe that a strongly positive Wassermann reaction always means syphilis.

To test the reliability of the Wassermann reaction in pregnancy the writer collected over a period of some months the bloods of ninety-four women, sixty-eight white and twenty-six colored, taken during the last three weeks of pregnancy, the women being dispensary and ward patients of Philadelphia hospitals. All of the tests were made in Dr. Kolmer's laboratory of the Polyclinic Hospital of the Graduate School of Medicine, University of Pennsylvania; some were done by the writer and the greater number by Miss Yagle, Dr. Kolmer's assistant. Two technics were carried out on every serum, Kolmer's standardized technic<sup>8</sup> and at the same time the ordinary technic, using three antigens, plain alcoholic extract of beef heart, the cholesterolized extract and the acetone insoluble lipoids. One negative test became very weakly positive after delivery. One blood negative by the ordinary technic and very weakly positive by the standardized technic was very weakly positive by both technics after the delivery of the patient. Two bloods very weakly positive by both technics, one blood negative by the ordinary technic and very weakly positive by the standardized, and one blood strongly positive (4-plus) by both technics remained unchanged in their reaction to the test after the patients



had been delivered. The postdelivery examinations were made from eight to twelve days after the birth of the babies.

The writer realizes that his series of Wassermann reactions are of negative value only. However, it would seem that if pregnancy is capable of giving rise to a falsely positive Wassermann reaction, at least one such case would have been present among ninety-four bloods tested. It is known that syphilis can exist in the presence of a negative Wassermann reaction. It is further known that under certain conditions a positive reaction will be developed in syphilis where it has previously been negative—the so-called provocative Wassermann. This being true it seems a reasonable supposition that where investigators have found a technically correct and truly positive Wassermann reaction in pregnancy which disappeared after delivery of the patient, the pregnancy has acted as a provocative to the Wassermann and the patient probably has latent syphilis.

#### CONCLUSIONS

1. In a series of ninety-four cases of pregnancy where the bloods were examined during the last three weeks of gestation, falsely positive Wassermann reactions with the Kolmer complement-fixation test for syphilis and with the ordinary routine technic were not observed.

2. If pregnancy is capable of producing a positive Wassermann reaction in the absence of syphilis, this condition should be encountered more frequently.

3. The few cases of apparently falsely positive Wassermann reactions in pregnancy recorded in literature may be provocative Wassermann reactions in cases of syphilis.

The writer begs to express his appreciation to Miss Yagle for her valuable laboratory assistance and to Drs. George Boyd, Richard Norris and Charles Cole for their cooperation in securing the specimens of blood.

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THE CLINICAL VALUE OF THE WASSERMANN REACTION:  
A COMPARISON OF THE CHOLESTERINIZED AND  
NOGUCHI ANTIGENS (ACETONE INSOLUBLE)\*†

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(Received for publication, March 5, 1922)

AS interpreted at present by the clinician the Wassermann test may be an instrument of great good or enormous harm, depending upon whether the clinician employs the test as an adjunct to the observations of his intelligence or whether he is content to allow a laboratory procedure, which is not infallible, to make his diagnosis for him.

There has been a great deal of discussion lately regarding the sensitiveness of the antigens used, reinforced with cholesterin, some holding that its specificity is not too great and that the percentage of false positives is low enough to be ignored; others claim that the antigen is too sensitive and does not become negative soon enough with treatment. We have also noticed that many are accustomed to base their conclusions as to the presence of syphilis upon the Noguchi antigen reaction (acetone insoluble), but in the department of syphilology in the Harper Hospital Out-Patient department we have come to the conclusion, after a long and careful study of our cases, that the reactions with the latter antigen are very unreliable, especially with regard to the very early cases, treated cases and latent and inactive cases. It is the purpose of this paper to analyze the Wassermann reactions obtained on 668 cases of all types, comparing the reactions obtained with both antigens.

As there is a normal amount of cholesterol in the blood which varies at times according to the presence of such diseases as diabetes, nephritis, jaundice, pregnancy, etc., Henes<sup>1</sup> believes that this varying amount of cholesterol together with the disease or condi-

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\*Read before the Wayne County Medical Society, Feb. 6, 1922.

†From the Out-Patient Department, Harper Hospital and the Buhl Memorial Laboratory.

tion present should be considered in interpreting the Wassermann reaction made with cholesterinized antigen.

Williams<sup>2</sup> found an increased blood cholesterol in 38 diabetics, but only one false-positive in 110 cases of nephritis, while 2 per cent of his cases had clinical or postmortem evidence that was not shown by the Wassermann reaction. He thinks that positive findings with a negative Wassermann or *vice versa* should be repeated at least once.

Rhamy,<sup>3</sup> using the ice box method, found that procedure to be 12.6 per cent more sensitive than the heat incubation, but Ray<sup>4</sup> thinks that a positive reaction using cholesterinized antigen alone should be given no specific significance in untreated cases presenting no clinical manifestations of lues and giving a negative history.

Larkin<sup>5</sup> found a higher percentage of positive and doubtful cases but does not recommend its use alone.

Kilduffe<sup>6</sup> in a résumé of recent literature on this subject thinks that all Wassermann reports should state the antigen used. He regards a 4-plus or 3-plus as an indication of syphilis, but lower reactions are only suspicious and should call for further investigation. He is a firm believer in the use of cholesterinized antigen and thinks that cases should remain under treatment until the cholesterinized antigen tests are negative.

Anderson<sup>7</sup> is also convinced that the cholesterinized antigen is more sensitive and the last to become negative, although it is true that it will not infrequently give a false positive reaction. He believes, however, that it is the most valuable antigen that can be employed as a guide to treatment.

The technic of the test and the method of preparation of reagents are as follows:

#### PREPARATION OF REAGENTS

Cholesterinized antigen is the alcoholic extract of normal human heart to which cholesterin has been added. The finely cut heart muscle is extracted in ten volumes of 95 per cent alcohol for one week in the incubator. It is then filtered and to 100 c.c. of the filtrate 0.2 gm. cholesterin is added and placed in the incubator overnight to dissolve the cholesterin. The antigen extract is diluted  $\frac{1}{10}$  by the slow addition of saline, titrated for antigenic, hemolytic, anticomplementary and specific properties, using a number

of known positive and negative sera. The amount used in the Wassermann test is four times the antigenic dose providing this amount is less than four or five times the anticomplementary dose. Inasmuch as antigen sometimes suddenly deteriorates, they are retitrated every two or three weeks.

Noguchi antigen is the acetone-insoluble portion of beef heart. Fresh beef heart muscle is finely ground and extracted with ten volumes of 95 per cent alcohol for one week in the incubator. It is then filtered, evaporated with the electric fan, the residue taken up in ether, and again filtered. To the filtrate ten volumes of acetone are added, allowed to stand a few minutes and filtered. The precipitate is a brown gummy mass to which is added just enough ether to dissolve. To 1 c.c. of the ether solution is added 6 c.c. of methyl alcohol. This is the antigenic extract. It is diluted with saline and titrated in the same way as cholesterinized antigen.

*Complement.*—Guinea-pigs are bled from the vessels of the neck into centrifuge tubes, the blood is allowed to clot and is placed in an ice chest until needed. The serum is then separated, diluted  $\frac{1}{10}$  with saline and titrated in the presence of each of the antigens used in the Wassermann test. After incubation at 37° C. for 15 minutes, the smallest amount which gives complete hemolysis is taken as the unit.  $1\frac{1}{2}$  units are used in the Wassermann test.

Amboceptor is the serum of a rabbit which has been immunized by the intravenous injection of 5 c.c. of 10 per cent washed sheep cells on each of four successive days. Five days after the last injection the animal is bled and the serum tested for amboceptor. If the titer proves one drop to 50 c.c. or more saline, the animal is bled aseptically and the serum stored in sterile ampoules ready for use. One unit of amboceptor is used in the Wassermann test.

Sheep cells, collected in citrate, are washed three times in saline and a 5 per cent suspension prepared.

All reagents are used in 0.5 c.c. quantities.

*Technic of the Wassermann Test.*—The patient's serum, free from cells, is inactivated in a water-bath at 56° C. for 30 minutes to destroy the natural complement. Sheep hemolysins are then removed by adding three drops of concentrated washed sheep cells to each serum and allowing to stand at room temperature for 10 minutes. Centrifuge and drop serum in varying quantities,—1, 2, and 4 drops for cholesterinized antigen, 2 and 4 drops for Nogu-

chi antigen, and 4 drops for serum control. Complement and antigen are mixed in equal quantities just before using and 1 c.c. of the mixture added to each tube. Incubate in water-bath at 37° C. for 30 minutes. Amboceptor and cells are mixed in equal quantities just before using and one c.c. of the mixture added to each tube. The temperature of the water-bath is kept at 37° C. and results are read in an hour and a half.

The amount of cholesterin added was not so great as that usually used, .2 per cent being employed instead of .4 per cent commonly advocated.

In considering the subject of syphilis it has always been a moot question whether the tests employed should be rendered more sensitive in order to detect the many cases of latent and inactive syphilis, or whether the tests were showing too many false-positives.

It has always seemed to us that real false-positives are not frequent, provided that due consideration is given to the physical examination of the patient himself, to his personal and family history. There is also unquestionably too great a tendency on the part of many to accept unhesitatingly the laboratory report regardless of symptoms, history or treatment, but oftentimes a serum will give a false-positive on the first test, although it will probably give a weaker positive or a negative on repeated examination. In this investigation a careful perusal of the histories of 493 out-patients of the Harper Hospital clinic was made and classified in one of several groups—hereditary, active (primary, secondary or tertiary), syphilis of the nervous system, latent, inactive and doubtful. One hundred seventy-five control cases are also included in the totals. In considering the hereditary cases, a division into active and inactive was also made, while the cases of nerve syphilis were all considered under the latent and inactive headings. The doubtful cases were those in whom no clinical evidence could be found, or anything in the history of the case suggestive of lues. Many were children on whom a test was done prior to tonsillectomy and the majority of these tests were not repeated. Others were children for adoption and careful consideration was given any degree of positive reaction. Included with the doubtful cases are a few cases that were entirely free from syphilis as nearly as we

could judge. These doubtful cases with their reactions will be discussed more fully later.

In order to arrive at any definite conclusions with regard to the comparative clinical values of the two antigens (alcoholic-cholesterin-reinforced and acetone insoluble or Noguchi) it was decided to consider the following points: 1. Reactions obtained with both antigens in active cases; 2. Reactions obtained with both antigens in latent and inactive cases; 3. A consideration of the reactions resulting in doubtful cases; 4. Reactions in cases that had had treatment before the first test; 5. Reactions after one or two courses of treatment; 6. A general consideration of cases presenting complicating diseases and those doubtful cases in which the test was repeated one or more times.

Any blood examination for syphilis, to be of any value, should give a positive reaction in active cases at least. Rarely, however, we see a case in which the reaction is negative with all antigens, but these cases are so few as to be a negligible quantity. In the present series the comparison between the two antigens can best be made by percentage as the cholesterinized antigen was used before the Noguchi and the summary of active cases shows many more tests with the former.

The active cases include all types—hereditary, primary, secondary and tertiary—and there were 71 reactions reported with cholesterinized antigen which were divided as follows:

+	- 1
++	- 2
+++	- 4
++++	- 64
Negative	- 0,

showing results which coincided almost perfectly with the clinical findings.

Using the Noguchi antigen only 20 reports were obtained on active cases, these being divided into:

+	0
++	3
+++	3
++++	10
Negative	4.

TABLE I  
ACTIVE CASES

REACTION	CHOLESTERINIZED ANTIGEN	NOGUCHI ANTIGEN
+	1	0
2+	2	3
3+	4	3
4+	64	10
Negative	0	4
	—	—
	71	20

20% false negatives with Noguchi antigen.

A comparison of these results will show that there were no false-negatives with the cholesterinized antigen while a few gave a somewhat weaker-positive than would have been expected. On the other hand only 50 per cent of cases showed as strong a positive with the Noguchi antigen as would have been anticipated, while 20 per cent showed complete hemolysis—an absolutely false-negative and in direct contradistinction to the clinical symptoms.

The greatest value of the Wassermann test should be in that great class of cases—the latent and inactive—in which there may be neither history nor clinical evidence to aid in making a diagnosis. It is in these cases that an antigen should be used that is sensitive enough to detect lues but not so sensitive that false-positives will result. The greatest number of our cases has been in the latent, inactive treated and cerebrospinal class and of necessity the reaction was of the utmost importance in making a diagnosis or as an indication for treatment. Most of these cases were known personally to us and in those not so known the histories were carefully examined to determine the presence of lues before classifying them as latent, inactive or cerebrospinal which are all considered together.

For the same reason as stated above there were more reactions reported with cholesterinized antigen than with the Noguchi antigen and the results appear to be overwhelmingly in favor of the former.

One hundred twenty-two reactions with cholesterinized antigen were reported as follows:

## Latent and Inactive Cases

+	- 3
++	- 1
+++	- 13
++++	- 94
Negative	- 11.

TABLE II

LATENT, INACTIVE TREATED AND CEREBROSPINAL CASES

REACTION	CHOLESTERINIZED ANTIGEN	NOGUCHI ANTIGEN
+	3	11
2+	1	10
3+	13	6
4+	94	14
Negative	11	35
	<hr/> 122	<hr/> 76

9% probably false negatives. 46% probably false negatives.

As these cases from the past history and clinical evidence were positive luctics at one time and nearly all without previous treatment, these results would show probably false-negatives amounting to 9 per cent. The weaker reactions (+ and ++) would be suspicious enough to make the diagnosis evident after the history has been investigated and would probably be a stronger positive after either potassium iodid or salvarsan.

Using the Noguchi antigen 76 tests were made and resulted as follows:

## Latent and Inactive Cases

+	- 11
++	- 10
+++	- 6
++++	- 14
Negative	- 35

Comparing these results with those obtained with cholesterolized antigen the value of each antigen is at once apparent.

With Noguchi antigen the percentage of weak-positives (+ and ++) was 27, with cholesterolized antigen only 3.3; the percentage of strong positives (+++ and +++) with the former was only 26, with the latter 87; while the negative tests, which in all prob-



ability were misleading, amounted to 46 per cent with Noguchi, but only 9 per cent with cholesterinized antigen.

These results would apparently give a great preponderance in favor of the cholesterinized antigen in selecting luetic cases among the latent and inactive or treated cases.

In order to determine what effect previous treatment had on the Wassermann reaction, all cases were collected which had had treatment of some kind. The interval of time varied in all cases ranging from a few months to several years and the amount of treatment also varied, including some arsphenamine or mercury or both. Fifty-four previously treated cases received a Wassermann test with cholesterinized antigen, fifty-two of these also having a Noguchi test done. Of this number the cholesterinized antigen gave 2 negatives and 5 weak-positives (+ or ++), but 47 strongly positive (+++ or ++++), showing that in 86 per cent of these treated cases the previous treatment had not affected the reaction when cholesterinized antigen was used. The result of the Noguchi antigen tests is quite different. Of the 52 cases, 30 were negative, 16 were a weak-positive (+ or ++) while only 6 were a strong-positive (+++ or ++++), a percentage of only 11 which were not affected by previous treatment.

TABLE III  
PREVIOUSLY TREATED CASES

REACTION	CHOLESTERINIZED ANTIGEN	NOGUCHI ANTIGEN
+	5	16
2+ }		
3+ }		
4+ }	47	6
Negative	2	30
	<hr/> 54	<hr/> 52
	86% not affected by former treatment.	11% not affected.

The effect of treatment on the Noguchi-Wassermann is still further shown by the tests made after one or two courses of treatment, each course consisting of four intravenous arsphenamine injections (0.6 gm. neoarsphenamine) and 12 mercuric salicylate injections (1 grain each) during a period of two months. Forty-

seven cases of both active and latent types gave a strong-positive (++++) on the first test; after the first course of treatment 26 were negative and have remained so, while two were ++ and two were still +++. It required two courses to produce a negative in 12 more cases, four being still ++ and one +++ at the end of the second course. In no case did the reaction remain a strong-positive with Noguchi antigen as it did in many cases with cholesterinized antigen.

TABLE IV  
DOUBTFUL AND NONLUETIC CASES

REACTION	CHOLESTERINIZED ANTIGEN	REPEATS	NOGUCHI ANTIGEN	REPEATS
+	3	1	6	0
++	22	3	7	0
+++	32	2	0	0
++++	47	0	0	0
Negative	6	14	93	20
	<hr/> 110	<hr/> 20	<hr/> 106	

As proof of the statement that cholesterinized antigen is not easily influenced by treatment and is the last to become negative, all 4-plus cases with this antigen were tabulated with this result:

Wassermann negative after 1 course	—	8
“ “ “ 2 courses	—	7
“ “ “ 3 “	—	13
“ “ “ 4 “	—	10
“ “ “ 5 “	—	2
“ “ “ 6 “	—	7
“ still positive after varying amounts of treatment—some taking only a few mercury injections, others as much as 3 or 4 courses		139
		<hr/> 186
Cases with 4-plus reactions not treated		31
		<hr/> 217

An analysis of the reactions obtained in doubtful and nonluetie cases throws some light on the question of false positives with cholesterinized antigen. Many of these cases were patients to be operated on—children for adoption, routine cases, etc., while 175

cases were control cases, medical students, interns, etc., in whom there was no history of syphilis.

TABLE V

EFFECT OF TREATMENT ON ACTIVE, INACTIVE, AND LATENT CASES OF ALL TYPES

	CHOLESTERINIZED ANTIGEN	NOGUCHI ANTIGEN
Wassermann negative after 1 course	8	26
“ “ “ 2 courses	7	12
“ “ “ 3 “	13	only four 2+ and
“ “ “ 4 “	10	one 3+ reactions
“ “ “ 5 “	2	after second course
“ “ “ 6 “	7	of treatment.
Wassermann still positive after varying amounts of treatment, some taking only a few mercury injections, others as much as three or four courses	139	
Cases with 4+ reactions not treated	31	
	217	

Of 110 doubtful and nonluetie cases, using cholesterinized antigen, 3 were +, 22 were ++, 32 were +++, 47 were +++++, 6 were negative. On the basis of considering positive only a 4+ reaction in doubtful cases this would be only 47 cases in 668 in which the test could be called a false-positive—a percentage of 6.5. Of 106 cases using the Noguchi antigen there were no false-positives, 93 cases were negative, 7 were ++, 6 were +.

A survey of these cases after a careful perusal of each patient's history and clinical evidence presented, shows that only 38 had a positive reaction that could, strictly speaking, be called a false reaction—a percentage of 5 out of the total of 668.

Our position on the question of reactions in doubtful cases is this—a strong positive (+++ or +++) reaction in the absence of all symptoms or history should be regarded as extremely suspicious and should be repeated one or more times before the presence of syphilis is finally determined. In this event a strong-positive must be repeated at least once before we consider the patient to be luetic. The weaker reactions (+ and ++) we consider suspicious and require them to be repeated for corroborative tests. It occasionally happens that a doubtful case will give a repeated ++ or +++ reaction, which is later substantiated by the therapeutic test, but these cases are very uncommon.

Regarding as highly suspicious those doubtful cases giving

a ++++ reaction, it was interesting to tabulate all the ++++ cases in this group that were clinically nonluetic. We found 44 cases that were ++++ with cholesterinized antigen; 39 of these with Noguchi antigen being negative, 3 being ++ and 2 were +. To illustrate the value and necessity of a repeated corroborative test 20 of these cases had a repeat test with this result—with Noguchi antigen all were negative; with cholesterinized antigen one was +, three were ++, two were none were ++++, fourteen negative. In this last group the percentage of false-positives was nil while the percentage before the repeat was six. A suggestion as to a possible reason for these reversals of reactions will be given when considering the complicating diseases.

Many of these cases had diseases of the skin, such as psoriasis, pityriasis rosea, lichen simplex chronicus, eczema, zoster, granuloma inguinale. These cases had with cholesterinized antigen, reactions varying from ++ to ++++, but repeat tests were negative. The case of granuloma inguinale was ++++ cholesterinized, negative Noguchi, but the patient was probably luetic before contracting the skin lesion.

Diseases such as jaundice, intestinal obstruction, rheumatism, thyroid disease, diabetes and myocarditis complicated cases having varied reactions with the first test, but the majority of those that were repeated were negative unless syphilis were present also.

If we are to believe that the amount of cholesterin in the blood is the determining factor in producing positive reactions, then the reactions during pregnancy can be little relied upon. Of eight pregnant cases the reactions were:

Cholesterinized		Noguchi
1	+	0
2	++	2
2	+++	0
3	++++	1
0	Negative	5
One case +++		++
After labor ++		Negative

The interpretation of reactions in pregnant women should be very carefully considered and should be repeatedly done in doubtful cases, even in different laboratories.

A large group of cases which gave confusing and contradictory results was the septic group comprising septic tonsils, osteomyelitis, antrum infection, general sepsis, tuberculosis, abscess, septic appendix and focal infections. Clinically these cases were all of the doubtful and nonluetic group and the first reactions were as follows:

Cholesterinized		Noguchi	2nd test 9 cases	
1	+	2	0	0
3	++	0	3	0
8	+++	0	0	0
14	++++	0	0	0
0	Negative	24	6	9

In many of these cases the septic focus was removed before the test was repeated and may have been a factor in the production of the first positive reactions.

Two cases had a +++ cholesterinized, negative Noguchi, but the father had a +++++, the mother a negative test. These would apparently be subjects for an investigation with regard to paternal hereditary syphilis. One mother with a +++++ test had two children giving a +++ and +++++ cholesterinized, negative Noguchi, but that combination is frequently encountered.

Three cases gave reactions which have not been accounted for—one case of Vincent's angina, one pregnancy, one suspected hereditary case. These reactions were alike in all cases—the first test was +++++; second was ++++; third was ++; the last was +. No explanation can be given at present for these changes, especially as they had no treatment.

#### CONCLUSIONS

In general we think that a positive Noguchi can be accepted as evidence of lues, but a negative reaction does not mean freedom from syphilis—our series showing 20 per cent of error in active cases, 46 per cent in inactive and latent cases. With cholesterinized antigen a negative reaction means syphilis-free, in active cases usually a +++++ can be expected, in latent and inactive cases a positive reaction of some degree is usual unless the patient has received a great deal of treatment. Latent cases show a probable 9 per cent of false-negatives.

Positive reactions in doubtful cases are rare with Noguchi antigen, but when obtained with cholesterinized antigen should be regarded as suspicious and call for repeated tests and further observation. In doubtful cases without history or symptoms a repeated ++++ reaction is necessary before definitely classifying that case as luetic.

In treated cases the reactions with cholesterinized antigen are not readily affected, but the Noguchi is easily influenced even by treatment a long time before. Even latency without treatment will give a large percentage of negatives.

Sera that are ++++ with Noguchi antigen are quickly rendered negative by treatment and rarely become positive again.

The cholesterinized antigen appears to us to be sensitive enough to pick out latent and treated cases, to be used as a guide to further treatment and to be of value in doubtful cases, provided repeated examinations are made and careful consideration given to the physical evidence and patient's history. We consider the false-negatives with Noguchi antigen to far outweigh the possible false-positives with cholesterinized antigen.

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# Abstract of Current Syphilis Literature

It is the purpose of this JOURNAL to review so far as possible all literature on syphilis as it appears in other medical periodicals and to present it in abstract form. Authors are requested to send abstracts or reprints of their papers to the Associate Editor, Dr. Grayson E. Tarkington, Dugan-Stuart Bldg., Hot Springs National Park, Ark.

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GRAYSON E. TARKINGTON, M.D., EDITOR.

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**Chemical Investigations of the Central Nervous System under Normal and Pathologic Conditions.**—Mathilde L. Koch, Ward's Island, N. Y. *Archives of Neurology and Psychiatry*, vii, p. 488.

Extensive chemical analyses of five parts of the central nervous system in two cases of uncomplicated general paralysis show the following changes as compared with normal controls: A tendency for the water and proteins to increase and for the lipoids as a whole to decrease. The extractives (water-soluble substances) are considerably increased, and, since the total solids have been very little changed, these probably compensate for the loss of the lipoids, especially the phosphatids. Of the lipoids, cholesterol shows a relative increase in all parts except in the cerebrum where it may be considered to be practically normal. The phosphatids (unsaturated lipoids of Fraenkel) show a consistent decrease presumably due to a disturbance in the lipolytic processes associated with the degeneration of the tissue. The cerebroside and sulphatids (saturated lipoids of Fraenkel) show less consistent changes. Since these are largely associated with the myelinated sheath (white matter), which showed less change on the whole in these brains than the gray matter, these have probably been less affected; the lipid phosphorus and lipid nitrogen were decreased, while the extractive phosphorus and extractive nitrogen were increased. Other chemical studies of nerve tissue (whole brain) in general paralysis check these findings: Pighini and Barbieri (Fraenkel method) observed in twelve cases of general paralysis an increase of water and proteins and a decrease in the total lipoids. The unsaturated lipoids were greatly decreased and the saturated lipoids, while decreased as a group varied among themselves. Cholesterol was increased. Smith and Mair found in three cases of general paralysis a decrease of lipoids (chloroform extract), and in fractionation of this chloroform extract, a marked decrease of the cerebroside the cholesterol normal and the phosphorus decreased. Nelson, who analyzed only one general paralytic brain, found the water and proteins increased and lipoids as a whole decreased. The extractives are probably increased. The lipid phosphorus and lipid nitrogen were decreased while the phosphorus and nitrogen in the extractive fraction were increased. These changes in general

paralysis present a chemical picture of lipoid degeneration, where the water and water-soluble substances have increased at the expense of the lipoids, especially the phosphatids. From a comparative study of different forms of insanity the author finds that general paralysis differs from dementia praecox, for example, in that the destructive changes in the former affect several constituents and not one constituent in particular, while in dementia praecox, W. Koch found an unmistakable decrease in the nonprotein neutral sulphur fraction in both the gray and white matter of the brain though the other constituents appeared practically normal. The cerebrum in these general paralytic cases shows perhaps the most consistent change in the different chemical groups, especially in the relative proportion of the lipoids to the extractives. The cortex shows a greater percentage variation from normal than the corpus callosum; the cerebellum and spinal cord show perhaps less changes than the cortex but more pronounced than the corpus callosum. Least of all affected parts was the corpus callosum.

**The Incidence of Syphilis in Hypothyroidism and Myxedema in Children.—**

Murray B. Gordon, Brooklyn, N. Y. New York Medical Journal, 1922, vol. cxv, p. 350.

There is little in the literature on the part syphilis can play in the causation of myxedema or hypothyroidism in children. Future studies of these conditions should be directed along lines which include serological and clinical investigations of patient and parents. No endocrine case report should be considered complete unless all modern scientific aids have been utilized in its study. Endocrinology will never be a scientific study until it is attacked by scientific methods. The results obtained in this series indicate syphilis is not of great etiological importance in the causation of either myxedema or hypothyroidism in children. It is, however, possible for syphilis to attack the thyroid gland with the production of these conditions. The presence of a mental deficiency in three of the five positive cases is significant of the predilection of the *Spirochete pallida* for the brain and nervous system.

**Syphilitic Hepatitis.—**Cornelius D. Briscoe, Ancon, C. Z. Proceedings of the Medical Association of the Isthmian Canal Zone, 1918, vol. xi, p. 45.

The symptoms are mental apathy, yawning, fever, accelerated pulse, moderate jaundice, more noticeable in the sclerae (in the negro), pain and tenderness over liver, which is somewhat enlarged, rarely a friction rub over the liver, and one or several of the common signs of tertiary syphilis enumerated above. There was no ascites in any of these cases. The digestion was interfered with in the early stage of the attack, i.e., there was loss of appetite, slight nausea, and as previously mentioned, rare vomiting. There was an increase in number of stools per day but no diarrhea. The most confusing element to be dealt with in the case is the elevation of temperature. The author has been unable to find in a textbook or recent literature anything which would aid in coming to a correct conclusion as to its causation; whether it is due to the toxins formed by the *T. pallidum*, or to a secondary infection of the gummata by the



colon bacillus, staphylococcus or streptococcus, or whether it is due to the irritation of common bile duct with subsequent retardation of the flow of bile or other infection. After examining the patient the first thing the author thought of was liver abscess, and indeed its differential diagnosis from that condition could not be made at once. A leucocyte count and differential were made but did not materially help. The leucocytes averaged about 15,000 per c.mm. and the polymorphonuclears were increased. The author knew that it was not the diffuse interstitial syphilitic hepatitis (cirrhosis) or other forms of cirrhoses, because the condition was too acute and there were lacking the signs common to those conditions. However, it was not until after he received the positive Wassermann reaction (two-plus) reports and saw the rapid response to antisyphilitic treatment that he was convinced that it was not liver abscess.

**The Clinical Aspect of the Initial Lesion of Syphilis in the Male.**—Norman M. Gibson and S. J. Wiley, Sydney, Australia. *The Medical Journal of Australia*, 1922, i, p. 123.

It is possible to make an accurate diagnosis of the primary syphilitic sore by clinical means alone in the great majority of cases. Direct microscopical examination of the sore is of considerable, but not primary importance being to some degree limited in its applicability and not invariable in its results. It is, however, sometimes the only method by which the nature of a syphilitic sore may be recognized. Thus it should always be employed, for it is obvious that the only sound method of diagnosis is to use with the knowledge that comes from experience, all the means available, both clinical and pathological. If direct microscopical examination of the sore does not reveal the spirochaete in a case definitely conforming to one or other of the clinical types, it is unjustifiable to wait for the appearance of the serological reaction; treatment should at once be instituted.

**The Role of the Microscope in the Diagnosis of Syphilitic Infection.**—R. W. Naylor, Toronto. *The Public Health Journal*, 1921, vol. xii, p. 481.

No observer can always diagnose a specific from a nonspecific lesion by clinical observation alone. The microscope affords the best means by which we can make the earliest accurate diagnosis of syphilitic infection. The earlier the diagnosis is made the more hope for a speedy and permanent cure. The best method of demonstrating *Spirocheta pallida* is by dark-field illumination, with stained films probably ranking second in importance. The diagnosis is only of full value when given by an observer who has had considerable experience in this work. A single negative examination has no special significance, several examinations should be made if necessary. Facilities of dark-field illumination under proper supervision should be available in every community. Our medical students, general practitioners, and the people at large should be studiously taught the importance of investigating, or of having investigated, any suspicious genital or extragenital sore for the presence of

*Spirocheta pallida*, if we ever hope to in any way control the transmission of syphilitic infection. Also they should be taught that the presence of gonococcal infection should stimulate them to investigate for possible syphilitic infection as well.

**Venereal Spirochetosis in American Rabbits.**—Hideo Noguchi, New York. The Journal of Experimental Medicine, 1922, vol. xxxv, p. 391.

Of 50 rabbits, otherwise regarded as normal, three adult females and two adult males (10 per cent) have been found to have in their genitoperineal region certain papulosquamous, often ulcerating lesions. A recently purchased group of twenty rabbits contained six females (30 per cent) with similar lesions. This condition runs a chronic course and is characterized by the presence of a spiral organism closely resembling *Treponema pallidum*. The rabbit spirochete has the same morphological features as *Treponema pallidum*; it is possibly a trifle thicker and longer than the average pallidum. Long specimens measuring  $30\mu$  are frequently encountered, and they show a tendency to form loosely entangled knots. A stellate arrangement of several organisms in a mass is frequently observed. In the lesion of one rabbit there were two types of spirochete, one of the variety just described, the other a somewhat coarser organism, closely resembling *Treponema calligyrum* found in a human condyloma, but a trifle thinner and longer. This organism is perhaps merely a variant type of the rabbit spirochete. The histological reactions are similar to, but considerably less cellular, than those occurring in typical primary syphilitic lesions. There is a marked hyperkeratosis and interpapillary infiltration not observed in scrotal chancre. The disease is transmissible to normal rabbits, in which the usual papular lesions can be readily reproduced in the genitoperineal region. In the first passages the incubation period varied from 20 to 88 days; subsequently one of the strains produced a lesion in 20 days on the second, and in 5 days on the third passage. No typical orchitis or keratitis was produced in the rabbits of the present series, although in one of the original rabbits scaly, papular lesions have developed on the nose, lips, eyelid, and paws. Monkeys (*Macacus rhesus*) failed to show any lesions within a period of 4 months after inoculation. In one instance transmission was accomplished through the mating of an infected female with a normal male. The Wassermann reaction was uniformly negative in the five rabbits with spontaneous lesions and in eighteen rabbits experimentally infected. Salvarsan had the same therapeutic effect on the lesions produced by the rabbit spirochete as on the experimental pallidum lesion of the rabbit.

**Method of Procedure in Treatment of Cases of Doubtful Initial Lesion—.**

Arthur Sayer, New York. Medical Record; 1921, vol. c, p. 192.

It is for the best interest of the patient, in all cases of doubtful initial lesion, to be sure of the diagnosis before commencing treatment. The doctor need have no hesitancy in delaying antispecific treatment, for the prognosis will be the same if the case is treated properly subsequently. By delaying treatment in doubtful cases until the dark-field is positive or the Wassermann is positive, some errors will be avoided and a lesion will often be proved to be other than a chancre.

The dark-field examination will be positive in all cases of chancre which are not treated locally with antiseptics, and three to five examinations will no doubt find the spirochete even in the most troublesome of cases. An effort should be made to find the bacillus of Ducrey, either by direct smear or culture in these cases, for the chancroid may in some cases simulate the chancre very closely. In herpes progenitalis there are usually one or more vesicles which disappear in a few days; the bases of the vesicles are not indurated and there is no glandular involvement present. Strange as it may seem, occasionally a case of scabies may fool an experienced observer. The penile lesion may be the only one noticed, and the patient give a history of exposure to venereal infection. Further observation of the case, however, will reveal the presence of other scabetic lesions (in the webs of the fingers, axillae, around the umbilicus) and the person later complains of itching.

**Incidence of the Wassermann Reaction in a Large Child-Caring Institution.—**

Louis H. Barenberg, New York, and Philip Rosenberg, Syracuse. *Archives of Pediatrics*, 1922, vol. xxxix, p. 23.

A group of Jewish institutional children were tested for syphilis. They varied in age from a few days to 6 years, and were unselected. Many had a family history or pathological conditions which would warrant a suspicion of syphilis. Eight hundred thirty Wassermann tests on 472 children were performed by the laboratories of the Department of Health of New York City, as well as that of the State. Without exception they proved to be negative. Three hundred ninety-nine luetin tests were performed on 350 of these children. Three hundred twenty-one reacted negatively, 3 positively and 26 were doubtful. The Wassermann tests on all children showing doubtful reactions were repeatedly negative. The 3 children showing positive luetin reactions showed at no time any clinical evidence of lues, and gave negative Wassermann reactions. The Wassermann tests on the parents of these children were likewise negative. Among the children tested, 22.4 per cent gave a history of insanity in one or both parents, 10.8 per cent were illegitimate, 6.5 per cent were mentally backward, 35.8 per cent showed various pathologic conditions. In spite of these circumstances, they all gave negative Wassermann reactions, a result which does not coincide with the reports of other workers. Contrary to the general opinion regarding the incidence of syphilis in child-caring institutions, the authors' results must lead them to conclude that among the children of the Jewish poor of New York City syphilis is an exceedingly rare disease.

**The Wassermann Test.—**L. B. Bull, Australia. *The Medical Journal of Australia*, 1922, vol. i, p. 172.

The Wassermann test is an empirical adaptation of a specific immunity reaction, but differs from such reactions in certain respects. As to the actual understanding and importance of these differences there is no general agreement. One view is that the Wassermann antigens now in use behave like specific antigens, because they are analogous to the disintegration products due to

the spirochaetes and that the reaction, therefore, conforms to all essential principles which govern true immunity reactions. An entirely opposite view is that it is merely a nonspecific physical or colloidal test based on the anticomplementary property common to a large variety of substances and that the test simply depends on the physical properties of syphilitic serum, which are such that an anticomplementary effect is more readily produced with it than without normal serum. The former view is used to explain the assumed specificity of "Wassermann substance" in relation to syphilitic infection and the latter serves to justify the need for arranging the test as a quantitative differentiation between the anticomplementary capacities of the serum of syphilitic, "borderline" and normal persons. At present the subject is too obscure for confident interpretation. Stated briefly, the problem of the Wassermann reaction is as follows: Normal fresh serum or complement dissolves red corpuscles when they are acted upon or sensitized by their specific antibody. Complement as a hemolysin may be neutralized by substances termed antihemolysins, which are of various kinds, the most important being (1) specific antigen-antibody combinations, (2) nonspecific biological products, such as tissue extracts, normal serum or egg-albumen, and (3) chemical compounds such as cholesterol. At least the second and third group and possibly the first, act in producing a reaction in syphilitic sera, while the second and third may produce a reaction in non-syphilitic sera if not adequately controlled.

**The Sigma Reaction for Syphilis.**—A. F. Rook, London. *The Lancet*, 1922, vol. ccii, p. 118.

The Sigma reaction for syphilis described by Dreyer and Ward is much simpler in technic than is the Wassermann reaction. The results of the series reported would seem to show that the results as regards blood serum tests in untreated cases are as good, or even slightly better than the results obtained by the Wassermann reaction, when judged from a clinical standpoint. The results obtained in the cerebrospinal fluid have not been so good as have the results of the Wassermann reaction. These cases are, however, so few that it is impossible to draw any inference from them. The test is easily standardizable, both as regards technic and reporting of results. Being a quantitative reaction it is possible that important information as to prognosis or the effect of treatment may result in the light of further knowledge.

**The Colloidal Benzoin Reaction of Cerebrospinal Fluid.**—Fanny Warnock, Chicago, Ill. *The Journal of Laboratory and Clinical Medicine*, 1922, vol. vii, p. 400.

Undoubtedly syphilitic cerebrospinal fluids do not regularly precipitate in any definite zone of dilutions. The benzoin reaction adds little in doubtful syphilitic cases. Tuberculosis meningitic cerebrospinal fluids do not precipitate the colloidal benzoin in any definite range of dilutions. Many nonsyphilitic cerebrospinal fluids do precipitate the colloidal benzoin suspension, and even precipitate it in the so-called syphilitic zone. Colloidal benzoin precipitation reactions

repeated on the same fluid do not give uniform results. The author's results are based on tests performed on a total of 87 cerebrospinal fluids, twenty-nine of which were diagnosed syphilitic, either clinically or from the laboratory standpoint, and fifty-eight of which were nonsyphilitic. Of the twenty-nine syphilitic spinal fluids twelve precipitated in the syphilitic zone. Each of them continued beyond that range. Of the fifty-eight nonsyphilitic spinal fluids fifteen precipitated in the syphilitic zone.

**The Luetin Test in Latent Syphilis.**—A. E. Van Nest, Detroit, Mich. *The Journal of the Michigan State Medical Society*, 1922, vol. xxi, p. 132.

The author has found luetin to be of a definite aid in the diagnosis of latent syphilis and feels that it should be used as routine as the Wassermann, in an effort to secure 100 per cent diagnosis of syphilis.

**On the Affinity of Sheep Corpuscles for Antisheep Hemolysin.**—R. L. Kahn and D. S. Lyon, Lansing, Mich. *The Journal of Infectious Diseases*, 1921, vol. xxix, p. 651.

A quantitative study of some factors which govern the affinity of sheep corpuscles for antisheep hemolysin was carried out. The hemolysin was obtained by immunizing rabbits with sheep corpuscles in the usual manner. The corpuscles employed were obtained interchangeably from 5 different sheep. A unit of hemolysin was taken to be the smallest quantity which completely hemolyzed 0.1 c.c. of a 5 per cent suspension of sheep cells in the presence of 0.1 c.c. of pooled guinea-pig complement after 15 minutes' incubation in the water-bath. In the first series of experiments, the rate of absorption of antisheep hemolysin by sheep corpuscles at different temperatures was studied. The extraction periods were 5, 10, 15 and 20 minutes, and the temperatures were water-bath, room and ice box. The hemolysin was extracted from both salt and pooled serum solutions. It was found when 0.05 c.c. quantities of packed sheep corpuscles were added to 1 c.c. quantities of either salt or serum solutions, each containing 400 units of hemolysin, that the difference in the quantity of hemolysin absorbed at extraction periods of 5 to 20 minutes were not marked. Neither were there large differences in the number of units absorbed at water-bath and ice box temperatures. In the second series, the effect of the concentration of hemolysin on the absorption capacity of 0.05 c.c. of packed sheep cells was studied. The extraction was in each case carried out for 10 minutes at room temperature. It was shown that the number of hemolysin units that this quantity of sheep corpuscles is capable of absorbing is directly proportional to the concentration of hemolysin. The largest number of units that 0.05 c.c. of packed cells absorbed in these experiments was 18,000. This number, however, does not represent the true absorption capacity of this quantity of sheep cells. The hemolysin serums employed, either undiluted or in low dilution, contained in every instance large numbers of hemagglutinins. These tended to bring about immediate precipitations of the corpuscles and thereby prevented proper contact

between the hemolysin and the cells. Finally, the effect of time and temperature on the hemolysin absorption capacity of 0.05 c.c. of packed sheep cells was studied. It was found that a 10 minute extraction period at room temperature was in most cases equivalent to a 1 hour or 2 hour extraction period at water-bath temperature. In a few cases, there was less extraction after 1 hour or 2 hours in the water-bath compared with 10 minutes' extraction at room temperature. This is believed to be due to dissociation of hemolysin and cells after prolonged extraction at 37.5° C. and also to the hemolysis of some corpuscles at this temperature with the liberation of some hemolysin.

**Comparative Values of the Complement Fixation Methods in Syphilis.**—Howard D. McIntyre, Emerson A. North, and Aurelia P. McIntyre, Cincinnati. The Ohio State Medical Journal, 1922, vol. xviii, p. 17.

Cholesterolized antigen properly prepared and titrated yields from 10 to 15 per cent more positive Wassermann reactions on luetic sera than does the plain antigen. The authors consider it a perfectly safe antigen to employ in the Wassermann reaction with complement fixation in the ice box at 2° C. for a period not longer than ten hours observing the precautions outlined in this paper. They have obtained but one positive reaction employing such methods in which the clinical findings, the history, or both, did not justify a diagnosis of lues. The Hecht-Gradwohl test when positive in the temperate zone is diagnostic of lues. It will yield 15 per cent more positive reactions on luetic sera than does the classical Wassermann reaction. It may be employed in from 95 to 98 per cent of fresh sera (not over forty-eight hours old). It does not yield false-positive results in tuberculosis. The Wassermann test employing complement fixation in the ice box at 2° C. will yield a much higher percentage of positive reactions than does the Hecht-Gradwohl test employing fixation in the water-bath. With complement fixation under the same conditions, however, the tests practically agree. The three serologic reactions appear in the serum and disappear under treatment in the following order: The ice box Wassermann reaction is the first to appear positive, the Hecht-Gradwohl test follows, the water-bath Wassermann reaction appearing last. Under treatment the water-bath Wassermann reaction disappears first, the Hecht-Gradwohl reaction next, the ice box Wassermann reaction last.

**Quantitative Relations Between Amboceptor and the Serum of Complement-deficient Guinea-pigs.**—Enrique E. Ecker, Cleveland, Ohio. The Journal of Infectious Diseases, 1921, vol. xxix, p. 611.

The serums of complement-deficient guinea-pigs have been studied and their deficiency as noted by Downing and Moore confirmed. The deficient action is not due to amboceptor interference because the increase of amboceptor leads to hemolysis of the cells. These serums when employed in comparatively small doses (0.1 c.c.) and in the presence of 500 units of hemolysin readily cause lysis. The deficient serums react in a similar manner as cobra venom inactive

serums in that the addition of normal inactive homologous or heterologous serums will markedly enhance hemolysis, confirming the results of Coca. Various inactive serums have varying degrees of activating power when added to the deficient serum amboceptor cell mixture. The same phenomenon was observed by Jonas in the case of cobra venom inactivated serum. By the increase of amboceptor and the addition of normal inactive homologous or heterologous serums the deficient serum has been made to act within the usual lytic range of normal guinea-pig serum.

**Notes on the Formalin Blood Test for Syphilis.**—C. Sufferin, M. A. Camb, England. *The Lancet*, London, 1921, vol. cci, p. 1107.

Out of 11 cases the blood tests agree in 8. Of the remaining 3 it is highly probable that two formalin tests were confused one with the other. In other words it is highly probable that the formalin results of these two cases really agreed with the Wassermann test results, making the total agreements 10 out of 11, or over 90 per cent.

**The Standardization of Suspensions of Red Blood Cells for Wassermann Tests.**—Joseph W. Bigger, Ireland. *The Lancet*, London, 1921, vol. ccl, p. 1369.

Methods usually adopted for making suspensions of red blood cells for the Wassermann reaction test are very rough, and the resulting suspensions vary greatly in strength. Such variations may introduce considerable error in the results of the test. A simple and rapid method of standardizing red blood cell suspensions is described. This method was controlled by counting the number of cells per c.c. in 12 suspensions, and was found to be accurate. It is suggested that the notation here adopted (in terms of Haldane's solution) might be used to record the strength of any suspension of red blood cells since a new suspension of similar strength could be prepared when required.

**The Interpretation of Serological Findings.**—Sterne Morse, New York. *The State Hospital Quarterly*, 1921, vol. vii, p. 20.

In the interpretation of serological findings which diverge among themselves and remain divergent after repetition one has several possibilities to consider, of which the following are examples. Positive cell count, negative Wassermann in the spinal fluid, positive blood Wassermann. In this situation syphilis in the central nervous system is probable, unless some other condition such as lethargic encephalitis or brain tumor is associated with systemic syphilis. Positive cell count, very faintly positive Wassermann in the spinal fluid (1 or 2-plus in the .5 c.c. dilution), negative blood Wassermann. Syphilis of the central nervous system is probable. Doubtful cell count (4 to 9 cells), faintly positive Wassermann reaction in the spinal fluid (1- or 2-plus in the .5 c.c. dilution), strongly positive blood Wassermann. Here also syphilis of the central nervous system is probable. Negative cell count, positive globulin, faintly positive Wassermann in the spinal fluid, positive blood Wassermann. In this

group syphilis of the central nervous system may be or may not be present, as such findings can apparently occur in systemic syphilis. It will, of course, be noted that the value of a faintly positive finding is small if not corroborated by the history or by physical signs, but is large if so corroborated. For instance, a single plus in the blood would have little value when obtained in a patient whose other serologic findings were completely negative and who showed no physical signs. Such a finding in the spinal fluid would still have only moderate value, although considerably more than that of the blood finding. But, such a finding would be of importance in a case under treatment, where a history of syphilis had been obtained, or where physical signs of syphilis were present. The course of the Wassermann reaction in cases of treated syphilis is a question which still needs further investigation.

**Neurosyphilis.**—H. Butts, U. S. N., and W. M. Alberty, U. S. N. United States Naval Medical Bulletin, 1922, vol. xvi, p. 483.

Involvement of the nervous system occurs at an early period of the disease. Early diagnosis and treatment are necessary to prevent later and more serious complications, such as paresis and tabes dorsalis. Spinal puncture should be made routine in every case of syphilis as early as the diagnosis is made, regardless of stages, and certainly before discharging the patient as cured. Many cases remain undiagnosed because of repeated negative blood Wassermanns, and in whom no examination of the spinal fluid has been made. No persistent case should be discharged from treatment until the intraspinal or intraventricular therapy has been instituted and strenuously administered.

**A Plea for the Early Diagnosis and Treatment of Cerebrospinal Syphilis.**—

D. A. Gregory, Sioux Falls, South Dakota. The Journal-Lancet, 1922, vol. xlii, p. 90.

Neurosyphilis is, to a great extent, a preventable complication of syphilis. Early diagnosis and treatment are necessary to prevent later and more serious syphilis. Lumbar puncture gives more real information regarding the presence or absence of cerebrospinal syphilis than all other neurological examinations. A cell count of over six, globulin increased with or without a positive Wassermann is, in a syphilitic, evidence of cerebrospinal involvement, even though other neurological examinations are negative.

**Notes on Mortality From Syphilis.**—Report on 1,183 Autopsies at the Central Islip State Hospital, Long Island, N. Y. Public Health Reports, 1921, vol. xxxvi, p. 3183.

There were 292 cases of general paresis and 30 cases of cerebral syphilis; i.e., 322 cases of syphilitic brain disease in 1,183 autopsies. The primary cause was given as some other condition in 73 of these 322 cases—an acute complication, as pneumonia, in 47; a chronic accompanying condition, as tuberculosis or chronic nephritis, in 20; a symptom, exhaustion, in 4; an incident,



cerebral hemorrhage and softening, in 2. Sixty-five other cases showed syphilis in quiescent form, as follows: Of 190 active cases of tuberculosis of the lungs, 19 occurred in combination with general paresis, of which number the primary cause of death was given as tuberculosis in 4, and as general paresis in 15. In 10 additional cases the presence of syphilis was satisfactorily demonstrated, either by clinical and pathological findings, or by a positive Wassermann reaction, although not appearing of sufficient importance to be given as the primary cause of death. Abdominal tuberculosis, in this series, was almost wholly secondary to tuberculosis of the lungs. In 46 cases, 1 showed the presence of quiescent syphilis. There were 37 deaths from cancer. Of 5 cases of cancer of the breast, 1 was in a case of general paresis. Of 6 cases of cancer of the female genital organs, 1 showed quiescent syphilis; and also 1 in 4 cases of cancer of the peritoneum showed quiescent syphilis. Of 6 cases of hypernephroma, 2 gave a positive Wassermann reaction. Two cases, both septic, of acute meningitis (total, 9) occurred in cases of general paresis. The poor nutrition, lowered resistance, and trophic disorders of general paresis, predispose to septic infection. Of 68 cases of purulent infection of all kinds, including general peritonitis and septicemia, 21 occurred in cases of general paresis, and 3 more in syphilitic cases. Of 24 cases of cerebral hemorrhage, 3 were due to syphilis of cerebral arteries. Of 21 cases of subdural hemorrhage, pachymeningitis hemorrhagica interna, 6 occurred in cases of general paresis, while of 35 cases of cerebral softening, focal degeneration, 4 were caused by syphilitic disease of the cerebral arteries. In 120 cases of diseases of the heart, 10 complicated general paresis, and in 4 of these the heart condition was given as the primary cause of death. Moreover, there was quiescent syphilis in 4 additional cases. There were two ruptures of the heart, in neither of which syphilis appeared as a cause. There were 224 cases of arteriosclerosis, and 6 of these complicated general paresis. Seven others gave a positive Wassermann reaction. In addition there were 10 cases of syphilitic arteriosclerosis. Of 8 cases of aneurysm of the aorta, syphilis was demonstrated in 1. One case of thrombosis of the abdominal aorta had a positive Wassermann reaction. Cirrhosis of the liver was a cause of death in 8 cases, with general paresis also present in 1 case and syphilis in another. In 32 cases of acute nephritis, 3 complicated general paresis, and 1 was syphilitic. Of 60 cases of Bright's disease 3 were in cases of general paresis and 6 others were in syphilitic subjects. Chronic nephritis was given as the primary cause of death in 9 cases of general paresis and cerebral syphilis. There were 5 suicides in the series; 1 was syphilitic.

**Incidence and Mortality of Congenital Lues at the Babies' Dispensary and Hospital of Cleveland.**—C. W. Burhans, Cleveland. *The Ohio State Medical Journal*, 1921, vol. xvii, p. 821.

In a series of 20,911 dispensary cases under three years of age, 1.05 per cent congenital lues have been found. The negroes, the white Americans and the Italians show a high incidence of congenital lues, while the Jewish race shows a very low incidence. The known mortality from all causes of 141 cases, followed where possible for three years, was 34.7 per cent.

**Syphilis: Its Relation to Infant Mortality and Child Welfare, With a Discussion of Present Day Method for Its Control.**—E. A. Morgan, Toronto. The Public Health Journal, 1921, vol. xii, p. 500.

In 1920 there were 13,300 births recorded in Toronto and 675 stillbirths. It was observed that the stillbirths were approximately 5 per cent of the live births—a proportion that is fairly constant in every country. Few figures are available which are of any help in arriving at an estimate of the number of miscarriages. They are probably twice as numerous as stillbirths, or 10 per cent, of the total live births—a conservative estimate. The total, therefore, for miscarriages and stillbirths is 15 per cent of the live births. That this figure cannot be very far astray is shown by statistics given by Adair. Of 2,773 pregnancies 2,422 ended at term and 351, or 14.5 per cent, terminated prematurely. The author has arrived at an approximate figure for the infant deaths due to syphilis by an estimate based on statistics of prevalence. Various estimates have been made of the prevalence of this disease among the infant population. Figures obtained from out-patient departments of hospitals on this continent, and admissions to the wards show a range of from 2 per cent to 6 per cent. Jenas believes that 5 per cent of the infant population is syphilitic. Of 725 successive admissions to the Medical Wards of the Hospital for Sick Children, Toronto, 29, or 4 per cent, were proven serologically and clinically to be syphilitic. Since the great majority of deaths due to lues occur in the first few months of life, whereas the majority of the hospital admissions are over that age, it is probable that considerably more than 4 per cent of all births are syphilitic. This would mean 665 luetic children born each year in this city, and of these at least 25 per cent, or 166, would die in the first year of life. According to these figures, syphilis would supersede bronchopneumonia as a cause of infant deaths in the first year and would take its place beside decomposition. If a syphilitic infant survives the first twelve months of life there is a much greater chance of his reaching maturity. Approximately 90 per cent of the deaths due to congenital syphilis occur in the first year. In the United States in 1915 there were 2,249 deaths under five years recorded as due to syphilis, and of these 2,022, or 90 per cent, occurred in the first year. As a rule, the second, third and fourth years are uneventful even in an untreated case. After this time various symptoms and signs, the so-called late or tertiary manifestations of hereditary lues, make their appearance and it is these manifestations that have an important bearing on the Child Welfare problem. The author has dealt with the problems of control under three headings; (a) the birth rate, (b) infant mortality, (c) child welfare. The two most important factors for consideration here are firstly, the education of infected adults and secondly, the treatment of pregnant syphilitic women. There is the treatment of the syphilitic infant as soon as symptoms of the disease appear. With the first evidence of snuffles the child should receive intravenous arsenical medication, alternated or combined with mercurial inunctions. The earlier treatment is instituted the better is the prognosis. Under the heading Child Welfare the author deals mainly with those children who have survived the first year. There are 60 cases in the series who have been under

treatment for a period of five months or more. Twelve, or 20 per cent, are apparently cured—that is, have had repeated, consecutive negative Wassermann reactions. Twenty, or 33.3 per cent, are markedly improved, that is, the Wassermann reaction has been reduced to a weakly-positive, and in some cases has fluctuated between positive and negative. Twelve cases, or 20 per cent, have been slightly improved and 16, or 26.6 per cent, have shown no improvement in the intensity of the Wassermann reaction.

**Chemical Studies of the Blood and Urine of Syphilitic Patients under Arsphenamine Treatment.**—Charles Weiss and Anna Corson, Philadelphia. *Archives of Internal Medicine*, 1922, vol. xxix, p. 428.

Five cases of tertiary syphilis with varying degrees of optic atrophy were studied. Small but definite increases in the nonprotein nitrogen of the blood (from 2 to 5 mg. per hundred c.c.) were observed three hours after practically every intravenous injection of 0.6 gm. doses of arsphenamine (ten out of twelve injections). These increases cannot be accounted for by the nitrogen content of arsphenamine (which is 5 per cent). The maximum rise accompanied the severest reaction. The increases in urea nitrogen were not always parallel to those in the nonprotein nitrogen and often were absent or exceeded them. Blood specimens examined at intervals after every injection of arsphenamine showed significant increases above the original limits, only in those cases in which the reactions were most pronounced. The nonprotein nitrogen in Case 1, which was from 24 to 30 mg. before injection, rose twenty-four hours after the injection to 44 mg. per hundred c.c. of blood. Case 2, with a less severe reaction, showed a milder increase (from 33.5 before, to 38.8 mg. eight days after injection). The urea nitrogen figures, however, remained normal. In no case was the final total nonprotein nitrogen or urea-nitrogen of the patient, when discharged (after one, two or three 0.6 gm. doses of arsphenamine) any higher than when admitted. On the contrary, many reductions were noted. All of the patients benefited greatly by the low protein diet and hospital care, as well as by the injections. Of the five cases studied, one had urea and total nonprotein nitrogen values distinctly above normal before treatment was begun. Yet this patient never showed untoward symptoms. On the other hand, Case 1, with normal blood figures, reacted severely. We cannot therefore, in every case, ascribe arsphenamine reactions to impaired kidney function alone. Marked but not pathologic increases in blood sugar occurred fairly constantly three hours after injection. Two or three times the authors noted that the blood sugars were doubled although no food had been taken during this interval. As a rule these increased values gradually subsided in the course of a few days. Whether these sudden increases were due to stimulation of the suprarenals, resulting from the action of the drug or from mere fright, is a matter to be investigated. Marked variations in blood sugar were also noted from day to day in specimens taken at the same hour before breakfast. The nervous state of the patient and the weather conditions seemed to be controlling factors. The uric acid of the blood was studied in Case 3 and it was found to be constantly normal during the investigation. In Cases 4

and 5 normal values were observed both before and during treatment. The amount of alkali added to acid arsphenamine to produce the disodium salt was insufficient to change either the bicarbonate reserve or the hydrogen-ion concentration of the plasma or of the urine. Ferannini draws similar conclusions from his pharmacologic studies of the respiratory rate in dogs. The elimination of phenolsulphonaphthalein was normal in each of the two patients studied although the former showed distinct signs of nephritis. There were no changes after arsphenamine treatment.

**Salvarsan-Jaundice: Its Causation, Incidence and Treatment.**—Frederick Chamberlain, London. *The Lancet*, 1922, vol. ccli, p. 733.

Facts and figures are quoted. From these facts and figures certain conclusions are drawn. The author suggests treating the liver as though it were an old lady of strong Tory views, intolerant of changes and any deviation from the normal course of events. If the patient be a miserable specimen do not hesitate to use salvarsan, preferably supplemented by intramine. If none of the rules are broken it is improbable that jaundice will arise. If it does occur, take the patient into a hospital or nursing home, supplement the general treatment with intramine, used at once and in full doses.

**Silver Arsphenamine in the Treatment of Syphilis.**—J. Barria de Medina, Madrid, Spain. *Archives of Dermatology and Syphilology*, 1922, vol. v, p. 321.

The author's opinion of silver arsphenamine is: Silver arsphenamine is one more brand of arsphenamine which may be employed in the cases in which it seems to be indicated. It can be used only by specialists, because it has disadvantages which will prevent its general use, and it, therefore, must occupy a secondary place in the treatment of syphilis; at least, so far as the general practitioner is concerned.

**Syphilis.**—James H. Stevens, Boston. *New York Medical Journal*, 1921, vol. cxiv, p. 592.

The syphilization of the people of the United States is progressing rapidly. Little can be expected of governmental supervision as long as our political system controls medical supervision. Until we can devise some simplification of technic which will place the treatment of primary syphilis in the hands of the general practitioner we shall not accomplish much by treatment. The author believes that this simplification may be an entering wedge which may be improved later with further simplification. There are fewer bad results in the use of arsenicals with the concentrated solution. Syphilis reacts to concentrated arsenicals just as rapidly as with the more dilute solutions. Reactions occurring with the concentrated solution are usually milder than by the more dilute solution. They come on at once if at all and so may be immediately treated. Adrenalin, in every case that shows reaction fifteen to twenty minutes before administration will prevent a repetition. The nitratoid

is the only type of reaction to be expected with the concentrated solution. Reaction once established in a patient will invariably recur thereafter without regard to dose unless adrenalin is used. This applies to a series only. After a rest of several months reaction may not follow in cases which previously reacted. The mercurials are of value when used to the point of tolerance and kept there. This can be done best either by mouth or by inunction. To expect results from most of the doses recommended is an absurdity.

**The Elimination of Arsphenamine and Neoarsphenamine in the Urine.—B.**

Barker Beeson and P. G. Albrecht, Chicago. *Archives of Dermatology and Syphilology*, 1922, vol. v, p. 51.

The Abelin test seems to be of real value. This opinion is quite generally shared by those who have employed it. In a recent personal communication Leredde again subscribes to this view. The slightly modified Abelin test, as employed by the authors, is readily and successfully applied for quantitative results without much difficulty or expense. The sensitiveness of the test is very great. It is only positive in the presence of arsphenamine and its derivatives, the quantity being approximately indicated by the color of the ring. Other clinical substances of the benzene series which may be eliminated did not furnish any positive reactions. Urine from cases of pneumonia, nephritis, rheumatism and gonorrhea did not furnish any positive reactions with this resorcin reaction. The elimination of arsphenamine and its derivatives by way of the urinary tract was slower in most of their cases than in Abelin's series. It was usually complete or nearly so within twenty-four hours after injection. A number of cases tested at later intervals gave, with the exception of those mentioned, uniformly negative findings. Elimination was especially prolonged in their cases of tertiary syphilis and neurosyphilis. The apparently early elimination of these drugs would seem in certain cases at least, to warrant a shorter interval between injections, as has been suggested by Pollitzer, Sicard and others. In cases of apparent nonelimination of the drug evidenced by a persistently negative Abelin reaction one should, as Leredde suggests, make a careful examination of the patient before continuing with the treatment. Elimination seems to be subject to the influence of a number of factors, among them: (a) the dose injected, (b) the solvent employed, (c) previous treatment especially by arsphenamine or its derivatives, (d) dietary indiscretion soon after treatment, (e) the personal element. Elimination does not always proceed in a rhythmical manner.

**Keeping Qualities of Market Samples of Neoarsphenamine While in Ampule.—**

George B. Roth, Hygienic Laboratory, U. S. P. H. S. *Public Health Reports*, 1921. Reprint No. 700, p. 3.

Commercial neoarsphenamine is a relatively unstable substance in ampule. Age, heat, and incomplete drying of the substance before ampuling are factors in causing deterioration in commercial neoarsphenamine. The deterioration of neoarsphenamine is shown by changes in color, mobility in ampule, toxicity,

solubility, and odor. The results of the experiments suggest (a) that inasmuch as neoarsphenamine may deteriorate within a short time after manufacture, and in order to secure further data on its keeping properties, the date of manufacture might be given on the label of all lots issued; (b) that neoarsphenamine should be kept under conditions similar to those required for vaccines; that is, at ice-box temperature.

**The Excretion of Arsenic After Serial Administration of Arsphenamine and Neoarsphenamine.**—Frank P. Underhill and Stanton H. Davis, New Haven, Conn. *Archives of Dermatology and Syphilology*, 1922, vol. v, p. 40.

Arsenic appears in the urine within a few hours after intravenous injection of arsphenamine or neoarsphenamine. The maximum excretion occurs on the day of or the day after injection. In a series of injections the maximum excretion is higher with each succeeding dose. In a series of injections the percentage of arsenic excreted is small in the first interval in both urine and feces, and increases in each injection with each succeeding dose and interval. Arsenic appears in the feces more slowly, but within three or four days after intravenous injection. In a series of injections the total percentage of arsenic excreted in the feces is larger than in the urine, being as high as 53.76 per cent in one week. There is no relation between the amount of arsenic excreted and the quantity of urine or feces. These facts are interpreted to mean that, in the early intervals of the serial treatment with arsphenamine and neoarsphenamine, the arsenic compounds are retained in the body up to a point at which the tissues are, as it were, saturated with them. When this point has been reached further additions of the arsenical preparations are in large measure quickly eliminated from the body. If this interpretation is correct, it would seem logical to modify the serial treatment to the extent that smaller doses may be given when the point of saturation has been reached, unless indeed it is at this point that the initial beneficial influence is exerted. Although further study is necessary before a positive conclusion may be drawn, it would appear that the point of saturation is attained at about the fourth injection.

**Arsenical Dermatitis During Treatment With 606.**—W. L. Harnett, Calcutta. *The Indian Medical Gazette*, 1921, vol. lvi, p. 441.

The conclusion which seems to follow from the author's figures is that the course of "606" laid down for the British army, though easily tolerated by the British soldier, is too intensive for the Indian soldier, who is on the average of lighter weight and build, and still more so for drivers, R. A. and followers, individuals of a lower standard of physique. An incidence of dermatitis of 0.3 per cent amongst British troops; 2.3 per cent amongst Indian sepoys, and 5.7 per cent amongst drivers and followers, seem to point to the necessity for mitigating the intensity of the course in proportion to the physique of the patient. When this was done by the substitution of intramuscular in-

jections of "914" for intravenous injections of "606" and the cessation of the intramuscular course of mercury, an immediate improvement was apparent, whilst the clinical and Wassermann tests were equally good. The generally accepted view that "914" is a drug of lower toxicity than "606" is also borne out by these observations. The importance of applying this principle in the treatment of syphilis amongst the civil population in India cannot be overemphasized. The drivers and followers referred to in this paper were recruited for the most part in the United Provinces and Central Provinces and were fairly representative of the lower classes of the population of those provinces. The value of routine courses of the arsenical preparations is very great, where large numbers of patients have to be treated but it is essential that the margin of safety in any such course should be very wide; the appropriate margin for any given class of patients can only be ascertained by experience.

**Note on the Technic of the Treatment of Syphilis.**—Theodore D. Reed, New York. *The State Hospital Quarterly*, 1921, vol. vii, p. 30.

It is very desirable in the intravenous administration of neoarsphenamine, more particularly in the insane, who may be disturbed, to administer the drug as rapidly as is compatible with good results. No unfavorable reactions have been noted by the author, following very rapid administrations. No unfavorable reactions, either symptomatically or in the blood have been noticed after giving neoarsphenamine in very high concentration, i.e., .9 gm. per 2 or 3 c.c. of double-distilled water.

**Comparative Values of the Antisyphilitic Drugs.**—H. E. Michelson, Minneapolis, Minn. *Minnesota Medicine*, 1921, vol. iv, p. 648.

In attempting to classify the various drugs, one must consider first, which drug has the most profound effect on the visible lesions of syphilis and can be given with the least danger to the patient. In the author's experience, arsphenamine and neoarsphenamine have about the same action on lesions which may be compared, occurring in individuals of about the same general constitutional characteristics. The author believes that retrogression has been slower with sodium arsphenamine and silver arsphenamine. Also, that mucous membrane lesions have been quite resistant to silver arsphenamine. However, the number of cases observed under sodium arsphenamine and silver arsphenamine is much smaller so that one might be inclined to compare the outstanding good results with the older drugs, with the poor results of the newer ones. The painstaking pathological studies made on animal subjects receiving arsphenamine and neoarsphenamine conclusively show neoarsphenamine to be the less toxic. Silver arsphenamine has been given in long continued courses and has probably been better tolerated when so employed than when the other members of the group were used over a long time. This very likely is due to the much smaller therapeutic dose. The effect of all of the antiluetic remedies in their action on

the Wassermann reaction is variable. The personal factor must be considered, and since the same individual cannot receive two drugs under precisely the same circumstances (age of infection, etc.) it is utterly impossible to make an accurate comparison. Nothing conclusive has been published to show that any member of this group of drugs possesses a selective action on any particular type of syphilis (cutaneous, osseous, neuro, etc.). The author believes that in all arsphenamine courses the patient must be carefully watched and questioned for early warning symptoms on the part of the organism against further amino-arsenicals and that the slightest significant symptom should cause the operator to delay subsequent injections in order to avoid grave accidents such as dermatitis, icterus, etc. Until more evidence is at hand the author most emphatically urges that mercury be used in connection with courses of any of the arsphenamines.

**The Antenatal Treatment of Congenital Syphilis With Salvarsan and Mercury.**—Leonard Findlay, Glasgow. *The British Medical Journal*, 1921, No. 3178, p. 887.

Antenatal or prophylactic treatment stands in marked contrast to the curative method, in that it at least attempts to influence the disease occurring during intrauterine life, and thus to cut short the loss of life from miscarriages and stillbirths. Galliot collected the statistics relating to 144 pregnant syphilitic women treated with salvarsan, and in only eleven, or 8 per cent, did the pregnancy not proceed to the birth of a child. Adams in the Thavies Inn Clinic has now treated 95 syphilitic mothers, and in all has obtained the birth of a living child. The author's series of pregnant women treated only consists of fifteen, but in only one did the pregnancy not terminate with a living child, and in that instance a difficult labor was the determining factor. Equally striking with the above is the fact that not one of the children, some of whom have been kept under observation for as long a period as seven years, has presented any clinical manifestations of the disease. In all the children, too, the Wassermann reaction was negative in infancy and early childhood, but in one, who reacted negatively during infancy, a weak-positive reaction was obtained at the age of 7 years, in the absence, however, of any clinical signs. When should the treatment be carried out? Is there a time of election? Should the treatment be carried out as soon as the diagnosis is made or should it be delayed till the woman is pregnant? In other words, "Are equally good results obtained irrespective of when the treatment is instituted?" The author usually selected the period of pregnancy partly because on theoretical grounds it seemed to him that the increased vascularity of the tissues—the endometrium—which we consider the locus of the invading spirochete, during that event will facilitate the influx of the spirocheticide. He also thought that the near approach of another possible syphilitic child would be an inducement for the mother to subject herself to the treatment.



**The Treatment of Neurosyphilis.**—W. H. Leake, Nashville, Tenn. The Journal of the Tennessee State Medical Association, 1921, vol. xiv, p. 245.

Syphilis of the nervous system is a current disease. No case of general syphilis should be pronounced cured until a complete examination of the cerebrospinal fluid has been made. Intraspinal serum therapy should not be attempted, except in selected cases, until the ordinary methods of treatment have been given a thorough trial. Syphilitic involvement of the central nervous system may occur in the primary stages as well as in the tertiary. Serum salvarsanized *in vivo* has a definitely spirocheticidal action, and is as efficacious and far safer than sera medicated *in vitro*. Spinal drainage following the intravenous administration of salvarsan or neosalvarsan has little, if any, advantage over simple intravenous therapy. From the standpoint of treatment each case of neurosyphilis presents an individual problem. Cases of early meningitis, later forms of neurosyphilis of the exudative type (cerebrospinal), and tabes offer the best prognosis. The treatment of paresis by any method has thus far been very discouraging. It is futile to attempt to influence symptoms produced by pressure or interference with nutrition. The strength of the Wassermann reaction in the spinal fluid should be titrated, otherwise it is impossible to judge accurately the effect of treatment on the reaction.

**Diagnosis and Treatment of Neurosyphilis.**—Lesley H. Spooner, Boston. Boston Medical and Surgical Journal, 1921, vol. clxxxv, p. 622.

Neurosyphilis is the result of the primary invasion by the Spirochete pallida. Changes in the spinal fluid, especially lymphocytosis, may be demonstrated before the appearance of physical signs of neurologic lesions. Spinal puncture should be employed in all cases of syphilis, before they are discharged as cured. This procedure should be done at least six months after cessation of treatment. Early diagnosis is most desirable and can be obtained not infrequently by spinal puncture only. Changes in cytology in the fluid can be shown to disappear under ordinary treatment. Many cases of established tabes and central nervous syphilis show improvement in symptoms and controlling laboratory findings under specific arsenical treatment. The intravenous method is advised and should be rejected only when ineffectual after fair trial. In the latter instance combined treatment is employed.

**The Treatment of General Paresis by the Intracistern Route.**—Franklin G. Ebaugh, Trenton, N. J. Archives of Neurology and Psychiatry, 1922, vol. vii, p. 325.

Intracistern injections of arsphenamized serum in the treatment of general paresis theoretically has some advantages over other methods. The facility of the operation makes it more practicable than intracerebral injections. The cisterna magna as a distributing center should promote a more widespread dissemination of serum. Complaints of the patients furnish no contraindication.

No reactions occurred. The operation is a safe clinical procedure. The author agrees with Ayer's landmarks and technic and his dictum that one should not perform cisternal puncture without preliminary experience on the cadaver. Cerebrospinal fluid pressure reductions were obtained following the intravenous injection of hypertonic salt solutions similar to those first described by Weed and McKibben. The clinical and serologic results in the cases treated seem to justify further use of this method.

**Syphilis in Children.**—H. Boyd Graham, Melbourne. *The Medical Journal of Australia*, 1922, vol. 1, p. 265.

Deep subcutaneous injection of novarsenobillon is regarded as a simple method of treatment generally applicable for all syphilitic children. The serious sequelae are the abscesses. Larger doses of novarsenobillon than are usually recommended have been given without untoward result. The general health of the children and active lesions have been beneficially affected by this method of using novarsenobillon. Percutaneous intravenous injections are preferable in selected cases.

## BOOK NOTICES

(Books for Review should be sent to Dr. W. H. Deaderick, Editor, Dugan-Stuart Bldg., Hot Springs, Arkansas.)

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**RADIUM THERAPY.**—By Frank Edward Simpson, A.B., M.D., Professor of Dermatology, Chicago Policlinic; Adjunct Clinical Professor of Dermatology Northwestern University Medical School; Attending Dermatologist to Mercy Hospital, Alexian Brother Hospital, Henrotin Hospital, etc.: Former President American Radium Society; Former Vice-Chairman, Section of Dermatology and Syphilology, American Medical Association; Director of the Frank Edward Simpson Radium Institute. 391 pages, with 166 original engravings. St. Louis, C. V. Mosby Co., 1922. Cloth, \$7.00 net.

The work consists of 21 chapters of which the first eight are devoted to a consideration of the general characteristics, origin, technic of measurement, absorption, penetration, and physical and chemical effects of radium on the body cells and organs. The radium reaction, therapeutic apparatus, dosage and the technic of radiation each receive a chapter. The practical application of radium in general surgery, gynecology, dermatology, otology, ophthalmology, rhinology and laryngology, the ductless glands and internal medicine is covered by ample chapters for each of these departments. The final chapter is devoted to professional injuries due to radium. The bibliography covers 58 pages and is one of the most complete in the English language. There are 166 original illustrations of the highest type of the engraver's art. These are used not only to show the clinical results of radium therapy but to elucidate technic and add greatly to the practical value of the work. The chapter on radium in dermatology occupies a space of 52 pages with many instructive and interesting illustrations. The author mentions seven groups of dermatosis in which radium offers a possibility of use. They are (A) Malignant tumors, (B) Benign tumors, (C) Chronic infections, (D) Inflammatory and granulomatous infiltrations of uncertain nature, (E) Hypertrophies, (F) Neuroses, (G) Disorders of the appendages of the skin;

(a) Sebaceous glands; (b) hair and hair follicles. Relative to Group D, the inflammatory and granulomatous infiltrations of uncertain nature, the author has the following to say, "In this group of dermatoses, radium is of considerable value. In psoriasis, lichen planus, lichen chronicus simplex, chronic eczema and lupus erythematosus, radium treatment offers, in selected cases, a great amount of relief. In psoriasis of the nails, radium is particularly useful. In obstinate patches of psoriasis that do not yield to ordinary measures radium may be used successfully. It must be remembered, however, that neither radium nor any other measure prevents recurrence of the patches." The book as a whole is splendidly written and well printed and is the most valuable recent contribution to radium therapy.

DIE SCHADIGUNGEN DER HAUT.—By Ullman, Oppenheim and Rille.

Conclusion of Vol. 1. 263 pages, illustrated with 108 engravings and 4 color plates. Leipzig, Leopold Voss, 1922. Paper. Price \$6.40.

Almost seven years have elapsed since the appearance of the first part of this volume (Vol. 1) of this two volume work. This part, completing Volume 1 has been delayed on account of the war. The eighteen chapters of this part include discussions by various authors of the general etiology and course of industrial skin lesions, history of occupational dermatoses, vocational stigmata of the skin, the pathology and symptomatology of skin changes produced by cold, occupational skin lesions due to the effects of heat, injuries to the integument by electricity, the experimental basis of the general pathology of the effect of light, symptomatology and course of superficial inflammations due to light, professional x-ray lesions, of the skin, those due to radio-active substances, injuries due to mesothorium, those due to compressed air, atmospheric influences upon the skin, tuberculosis of the skin in industry, skin changes due to work in domestic animals, leg ulcers in relation to occupation, epitome of laws and ordinances relating to the protection of laborers, and typical injuries to the skin and soft parts. The chapter on leg ulcers was written by Ravogli of Cincinnati. The text illustrations are well executed and the seven colored plates are of the highest order of skill. The work should prove of much value to those interested.

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